STEREOSELECTIVE SYNTHESIS OF (*E*)-ENOL BORINATES VIA BORYLATION OF LITHIUM ENOLATES

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by

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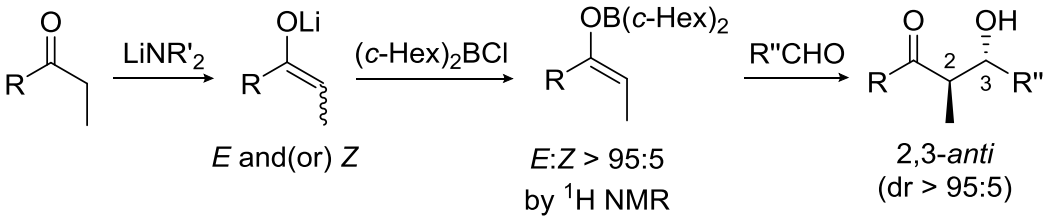
Abstract

Aldol reactions of enol borinates constitute one the most powerful and reliable methods for asymmetric synthesis. Crucial to this success is the stereoselective preparation of enol borinates and ‘soft enolization’ is by far the most popular method; however, limitations in substrate scope have been reported, particularly with sterically hindered ketones and those incompatible with the Lewis acidic reagents. Borylation of lithium enolates was found to be a general and efficient approach to enol borinates that can overcome many of the above limitations. Under appropriate conditions, the (*E*)-enol borinate is produced with high diastereoselectivity regardless of the starting geometry of the precursor Li enolate. The mechanism of the underlying isomerization process is unusual. The method has been implemented successfully across a range of ketone substrates and is complementary to ‘soft enolization’ with the advantages that reactivity is dependent on lithium enolate formation and stereoselectivity is independent of the geometry of lithium enolate.



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List of Abbreviations

ap	apparent (NMR signal)
Ar	argon
atm	atmosphere(s) (as a measure of pressure)
aq	aqueous
anti and *syn*	notations for relative configuration of the two new stereocenters in the aldol product. The carbon chain that contains the two stereocenters is drawn in a zigzag fashion. In the *anti* isomers one of the substituents is directed toward the viewer, the other one away from the viewer, or vice versa. In the *syn* isomers both substituents at the stereocenters are directed either toward or away from the viewer.
9-BBNCl	9-Borabicyclo[3.3.1]nonyl chloride
9-BBNOTf	9-Borabicyclo[3.3.1]nonyl trifluoromethanesulfonate
Bn	benzyl
br	broad (description of a spectral signal)
t-Bu	*tert*-butyl
n-BuLi	*n*-butyllithium
Bu_2BOTf	dibutylboron trifluoromethanesulfonate
°C	degrees Celsius (temperature)
^{13}C NMR	carbon 13 nuclear magnetic resonance
δ	NMR chemical shift in parts per million downfield from TMS
d	doublet (spectral signal)
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N*,*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
dr	diastereomer ratio
E and *Z*	configurational descriptors for alkenes. *E* denotes that the substituents of highest CIP (Cahn-Ingold-Prelog) priority at each end of the double bond are on

	opposite sides. If the pertinent substituents are on the same side, the descriptor is *Z*.
Et	ethyl
EtOAc	ethyl acetate
FCC	flash column chromatography
h	hour(s)
c-Hex	cyclohexyl
HMDS	hexamethyldisilazane
^{1}H NMR	proton nuclear magnetic resonance
H_2O_2	hydrogen peroxide
MHz	megahertz
min	minute(s)
Me	methyl
OTf	trifluoromethanesulfonate (triflate)
i-Pr	isopropyl
rt	room temperature
sat	saturated
THF	tetrahydrofuran
TLC	thin layer chromatography

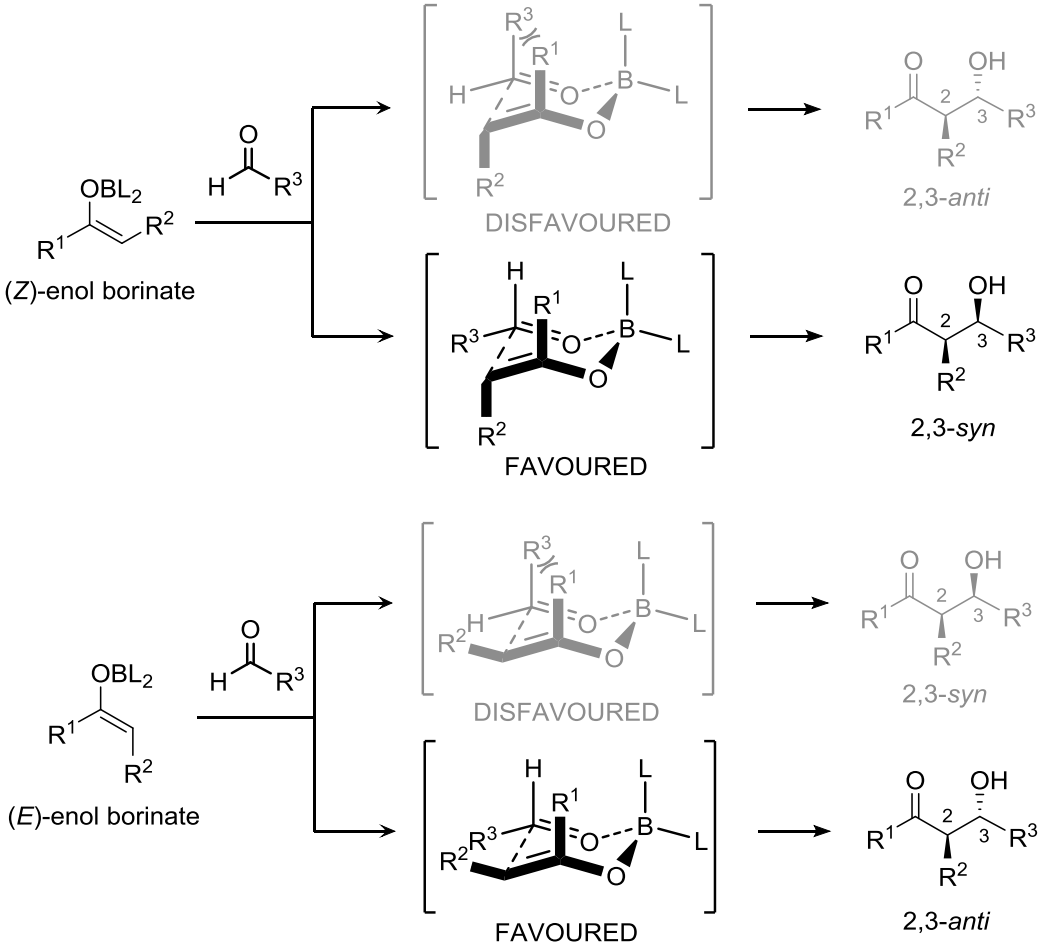
1 INTRODUCTION

The aldol reaction has long been recognized as one of the most useful synthetic tools for stereoselective carbon–carbon bond formation. Under 'traditional' aldol reaction conditions, in which acidic or basic media are usually employed, dimers, polymers, self-condensation products, or α,β-unsaturated carbonyl compounds are invariably formed as by-products.[1] The 'directed' aldol reaction uses a preformed metal enolate and is regarded as a versatile strategy for avoiding the formation of these by-products. The generation and reactions of different metal enolates have been extensively studied and countless successful applications have been reported.[2] Among those, enol borinates have been recognized as being particularly powerful for the efficient synthesis of β-hydroxy carbonyl compounds.[3-5]

1.1 Enol borinates and aldol reaction of enol borinates

Enol borinates were shown to be efficient intermediates for addition to carbonyls in cross-aldol reactions. The relative configuration of the new stereogenic centers formed in the reaction of enol borinates with aldehydes is a direct consequence of the enolate geometry, with (*Z*)-enol borinates affording the 2,3-*syn* aldol products and the (*E*)-enol borinates leading to the 2,3-*anti* isomers (Scheme 1-1).[4] The reaction of enol dialkylborinates with aldehydes occurs via a 'closed' transition state formed by pre-complexation of the boron with the carbonyl. These complexes have relatively short metal–ligand and metal–oxygen bonds, thus, facilitating the formation of tight, well-organized chair-liked transition states where R^3 occupies a *pseudo* equatorial position (Scheme 1-1). As a result, aldol reactions via enol borinates generally produce aldol products more stereoselectively than those via alkali metal enolates such as Li enolates.

Scheme 1-1. Rationalization for stereoselective aldol reaction of enol borinates and aldehydes.



Because of the strong correlation of the relative configuration of the aldol products with the geometry of the enol borinates, thereby enabling *syn*- as well as *anti*-configured aldol products to be made as desired, the use of enol borinates is a very powerful synthetic tool for assembling the stereochemically complex backbone of many natural products (Figure 1-1).[6-8]

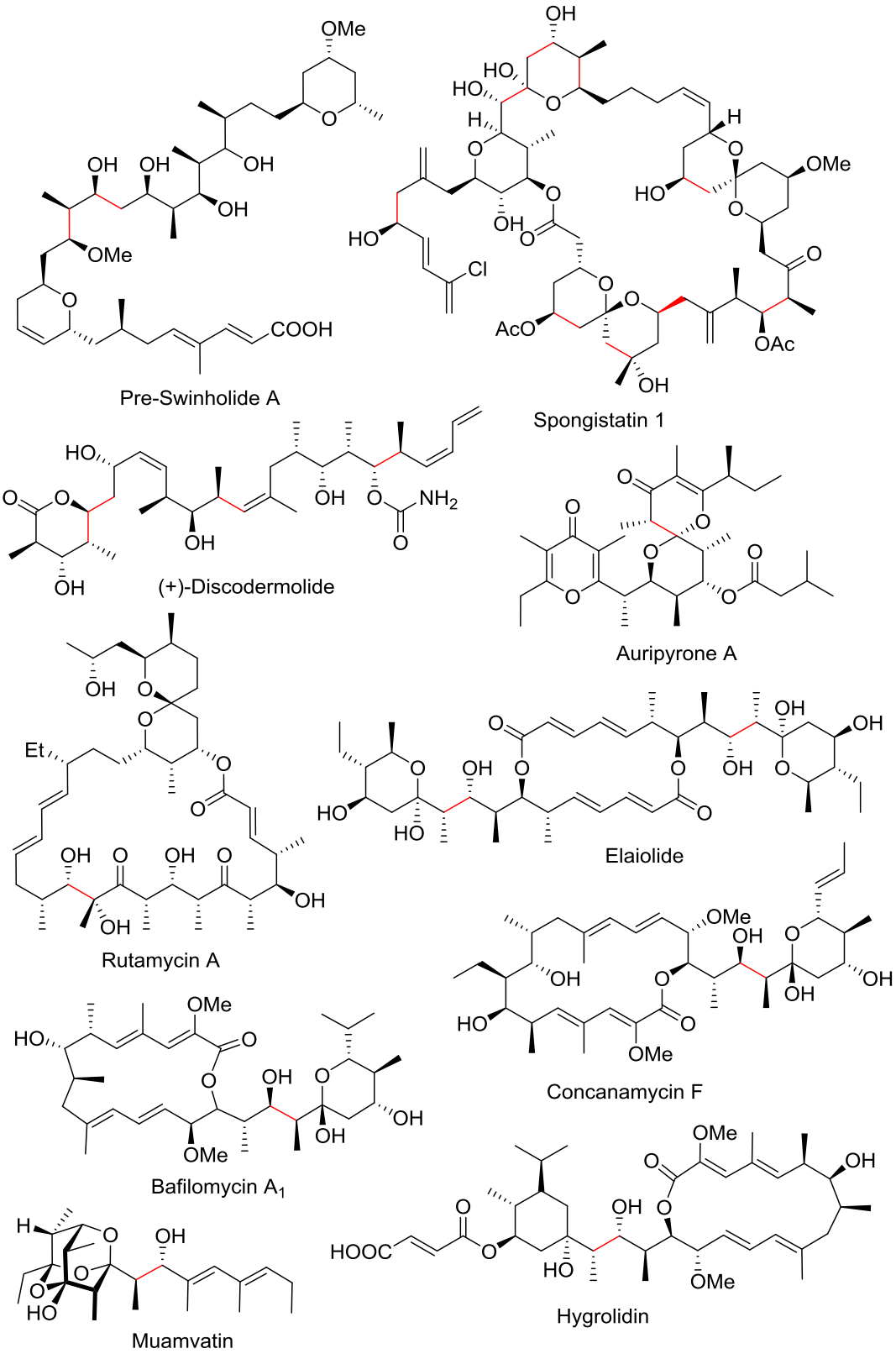


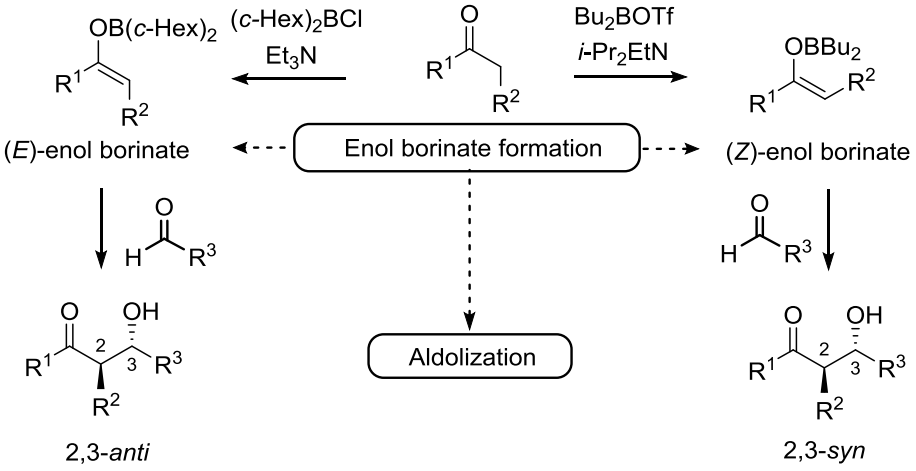
Figure 1-1. Examples of natural products where enol borinates have been used in their total synthesis.

1.2 Generation of enol borinates

1.2.1 Soft enolization

Because the relative topicity of aldol addition is directly correlated to the enol borinate geometry, stereoselective preparation of the enol borinates is crucial to the success of this process. Although there are several synthetic routes to enol borinates,[9, 10] the most popular approach by far involves 'soft enolization'; i.e., treatment of carbonyl compounds with a dialkylboron halide or triflate in the presence of a teriary amine.[5] Stereoselective synthesis of (*E*)- and (*Z*)-enol borinates can be achieved from ketones, esters, and thioesters. In case of ketones that are unbranched at at least one of the α-positions, stereoselective methods to achieve either diastereoisomer have been established. The (*Z*)-enol borinate is synthesized selectively using a combination of small ligands on boron (e.g., butyl) with a good leaving group (e.g., –OTf) and use of a bulky tertiary amine (e.g., *i*-Pr_2EtN) at low temperature. In contrast, the (*E*)-enol borinate can be prepared with high selectivity using sterically demanding ligands on boron (e.g., *c*-Hex) with a relatively poor leaving group (e.g., –Cl) and using a less hindered amine base (e.g., Et_3N) (Scheme 1-2).[3-5]

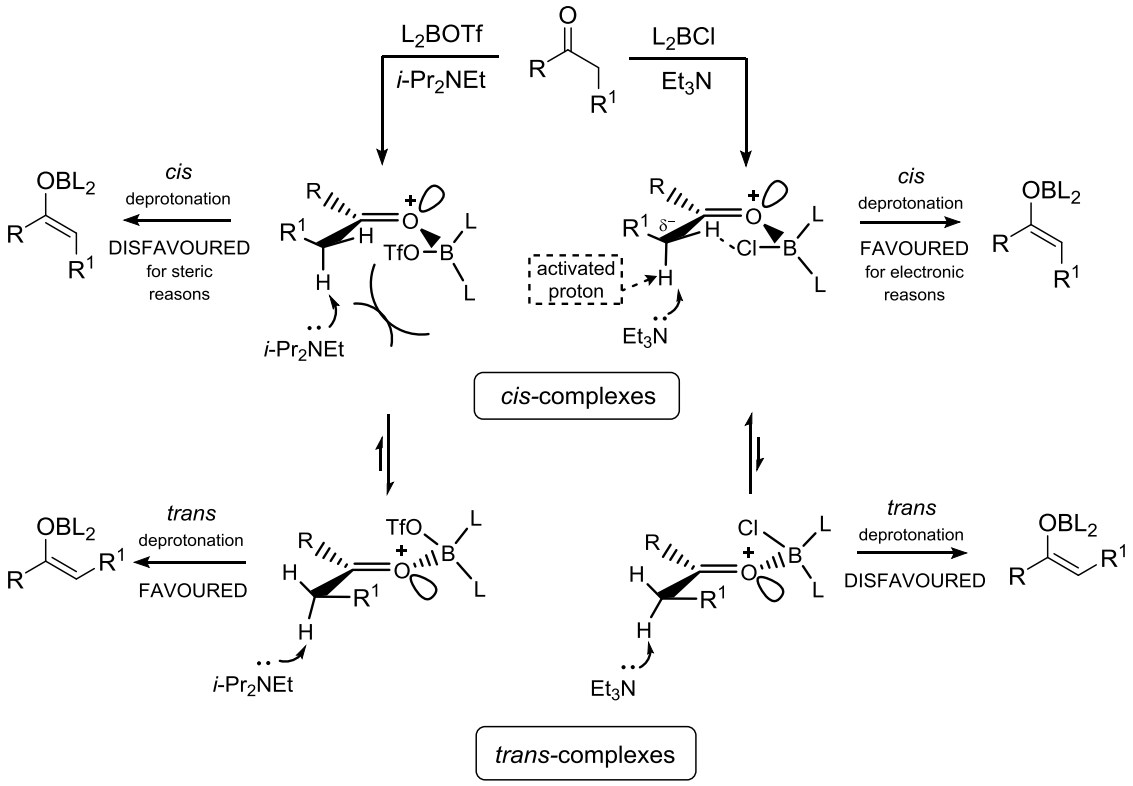
Scheme 1-2. Stereoselective formation of enol borinates via 'soft enolization'.



Even though there were different mechanistic explanations[11, 12] proposed for the observed stereoselectivity in soft enolization, the rationale reported by Paterson *et. al.*[13] is most commonly accepted.[10] The proposed sequence involves coordination of the L_2BX reagent to the carbonyl compound with either of two possible geometries (*cis* or *trans*) (Scheme 1-3). In the *cis*-complexes, the B-O bond is oriented *cis* to the bond connecting the α-carbon and the carbonyl group. The substituent on the α-carbon ($–R^1$) orients itself away from the carbonyl to minimize the

interaction with the boron ligands. In the *trans*-complexes, the B-O bond is oriented *trans* to the unbranched α-carbon. These conformations in the initially formed complexes, along with the use of proper tertiary amine and leaving group, influence the stereocontrol in the subsequent rate-determining deprotonation step.

Scheme 1-3. Paterson's model for rationalization of stereoselective formation of boron enolates by 'soft enolization'.



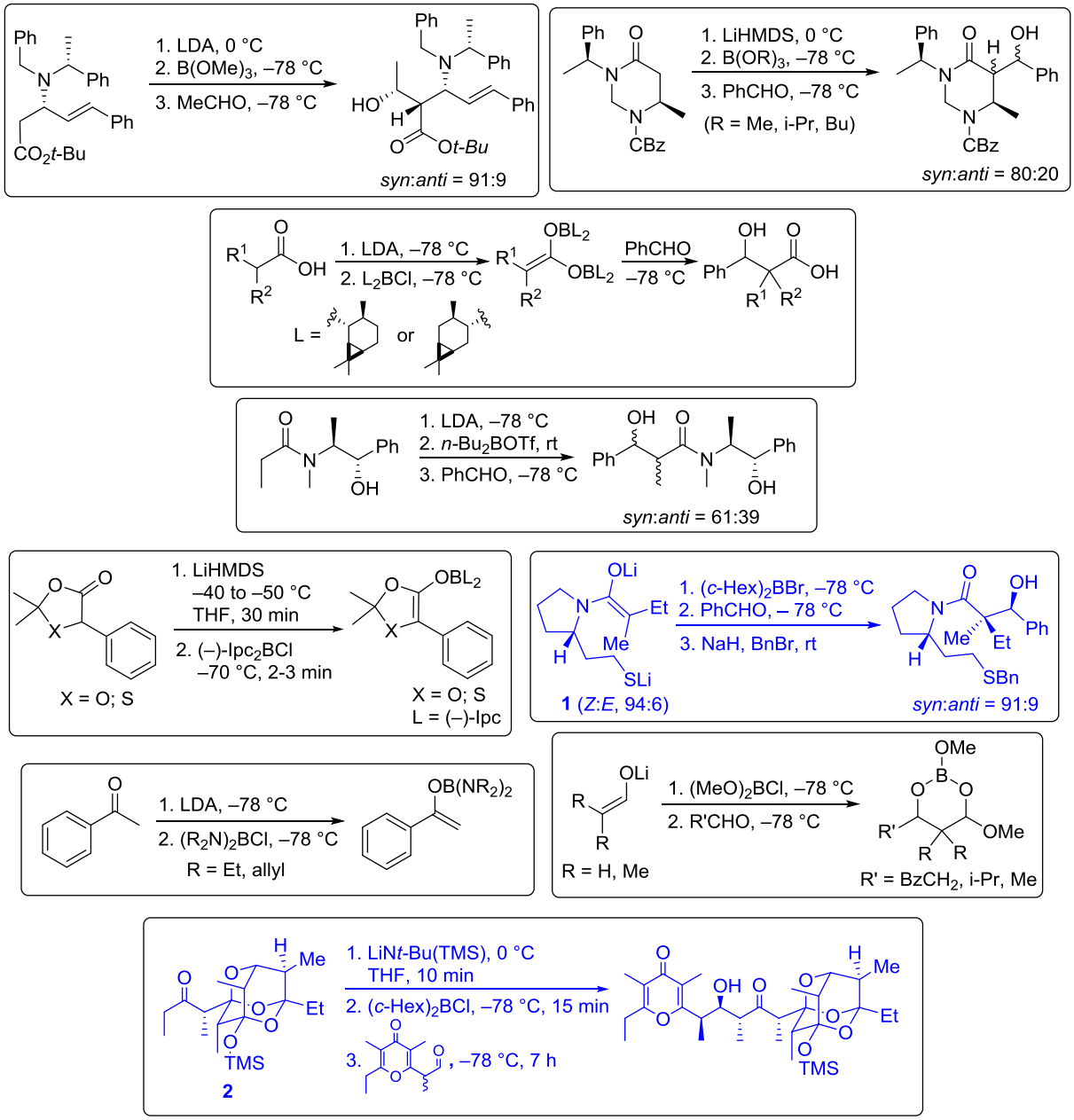
The proposed mechanism is commonly accepted because it can rationalize several observations at once. As shown in Scheme 1-3, with bulky leaving groups such as triflate and iodide, and a bulky amine, deprotonation via the *cis*-complex is disfavoured due to steric hindrance between these bulky groups and the amine; hence, deprotonation via the *trans*-complex predominates, affording the (*Z*)-enol borinates. With relatively small bridging ligands such as chloride, the Cl atom is directed towards one of the hydrogens on the *cis* α-carbon in the *cis*-complex, which induces a partial negative charge on this α-carbon and activates the proton antiplanar to the carbonyl for deprotonation by an unhindered base like Et_3N. Under these circumstances, amine deprotonation leads to the (*E*)-enol borinates. An increase in the steric bulk of the R^1 group or of the ligands at boron (L) also favors the formation of the *cis*-complex leading to (*E*)-enol borinates.

Alternatively, an increase in the steric interaction between R^1 and R is better sustained by the *trans*-complex because the *cis*-complex would be destabilized by the interaction between R^1 and R; hence, deprotonation leads to (*Z*)-enol borinates predominantly.

1.2.2 Borylation of lithium enolates

Despite the tremendous success of the 'soft enolization' approach to enol borinates, limitations of the method include sterically hindered ketones[14] and substrates incompatible with Lewis acidic borylating reagents,[3] in addition to limited choices on varying the boron ligands. Due to these limitations, alternative methods may be required to successfully obtain the desired enol borinates. Borylation of lithium enolates is an approach to overcome the limitations of 'soft enolization'. Scattered examples of borylation of Li enolates from carboxylic acid derivatives[15-20] and ketones[21-23] have been reported (Scheme 1-4). The stereoselectivity for enol borinates formation in most of these reports was either not discussed or not applicable. However, it is noteworthy that in the borylation of amide-derived lithium (*Z*)-enolate **1** followed by subsequent aldol reaction, the *syn*:*anti* (91:9) selectivity in the final products is very close to the *Z*/*E* ratio of the intermediate lithium enolate (94:6, *Z*:*E*) (Scheme 1-4).[20] Consistent with this observation, borylation of LiN(TMS)(*t*-Bu)-generated lithium (*E*)-enolate of ketone **2** followed by aldol reaction gave *anti*-product predominantly.[23] These two results suggested that the borylation of lithium enolates to enol borinates can occur under mild conditions with retention of the enolate configuration.

Scheme 1-4. Reported examples of enol borinate formation via borylation of lithium enolates.



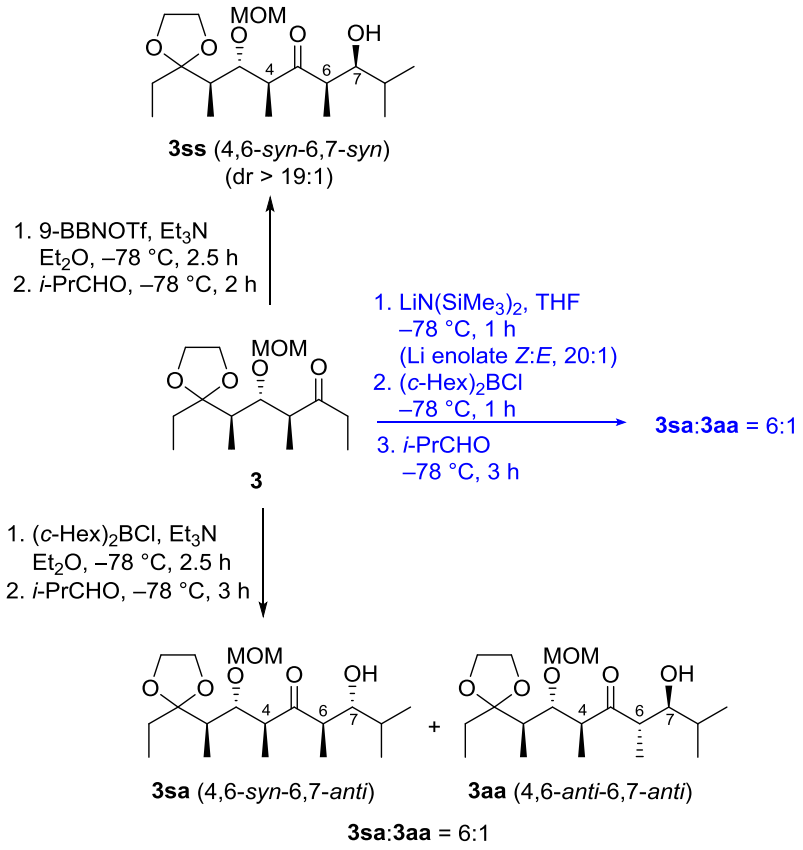
1.3 Previous research formation of (*E*)- or (*Z*)-enol borinates by borylation of lithium (*Z*)-enolates

1.3.1 Preliminary observation

The study on borylation of lithium enolates in Ward Group began with a serendipitous observation made by M. Biniaz,[24] where only aldol products **3sa** and **3aa** arising from an (*E*)-enol borinate were obtained after reaction of lithium (*Z*)-enolate of **3** with (*c*-Hex)$_2$BCl followed by

addition of *i*-PrCHO (Scheme 1-5). The selective formation of 6,7-*anti* adducts **3sa** and **3aa** suggested that stereoselective formation of the (*E*)-enol borinate of **3** had occurred during the borylation step. Because literature reports suggested that borylation of lithium enolates to enol borinates can occur under mild conditions with retention of the enolate configuration,[20, 23] isomerization of the newly formed (*Z*)-enol borinate to (*E*)-isomer was proposed to explain this observation.

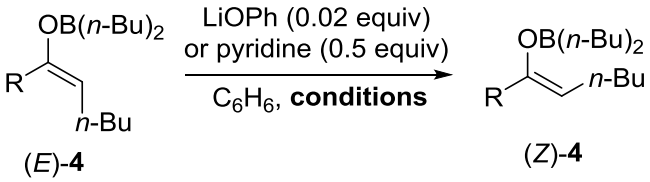
Scheme 1-5. Serendipitous observation of highly selective formation of (*E*)-enol borinates.



1.3.1 Isomerization of enol borinates

Except for enol borinates bearing halogen ligands on the boron atom, enol borinates are well known to be thermally stable and can be stored for long periods without significant decomposition;[10] however, *E*/*Z* isomerization to the equilibrium mixture is observed in some cases when the compounds are kept at or above room temperature. Reported isomerizations of ketone-derived enol borinates have involved rather harsh conditions. Masamune reported that a catalytic amount of lithium phenolate or pyridine slowly isomerized enol borinate (*E*)-**4** to the (*Z*)-isomers at ambient or high temperature (Table 1-1).[25]

Table 1-1. Masamune's procotol for isomerization of **4** via lithium phenolate and(or) pyridine mediated isomerization.

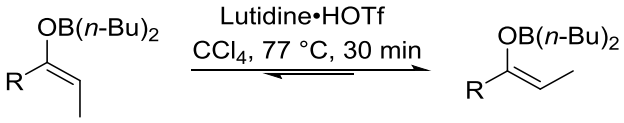


(*E*)-**4** (*Z*)-**4**

R	isomerization conditions	yield of (*Z*)-**4**
$-CH_3$	LiOPh (0.02 equiv), 16 h, 22 °C	84
$-CH_2C_6H_5$	LiOPh (0.02 equiv), 16 h, 22 °C	81
$-C_6H_5$	LiOPh (0.02 equiv), 8 h, 50 °C or Pyridine (0.5 equiv), 24 h, 80 °C	88

Evans *et al.* reported that enol borinates **5** of ethyl ketones were configurationally stable at 25 °C for as long as 2 h in the presence of the DPEA•HOTf and at 0 °C (30 min) in the presence of lutidine•HOTf. At elevated temperatures (77 °C, $CC1_4$) complete enolate equilibration (*E* ↔ *Z*) could be achieved (Scheme 1-6).[12]

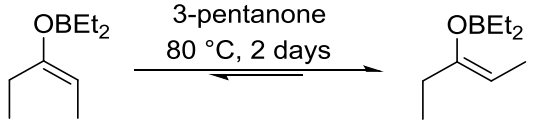
Scheme 1-6. Evan's protocol for isomerization of enol borinates.



(*E*)-**5** **5a** R = Et : *E*:*Z* = 14:86 **5b** R = *i*-Pr : *E*:*Z* = 27:73 (*Z*)-**5**

Köster *et al.* also reported that ketone-derived enol borinates **6** can be isomerized in the presence of 3-pentanone. The equilibrium was reached after heating the mixture of (*Z*)-**6** and 3-pentanone at 80 °C for 2 days (Scheme 1-7).[26]

Scheme 1-7. Reported isomerization of enol borinates in the presence of ketone.

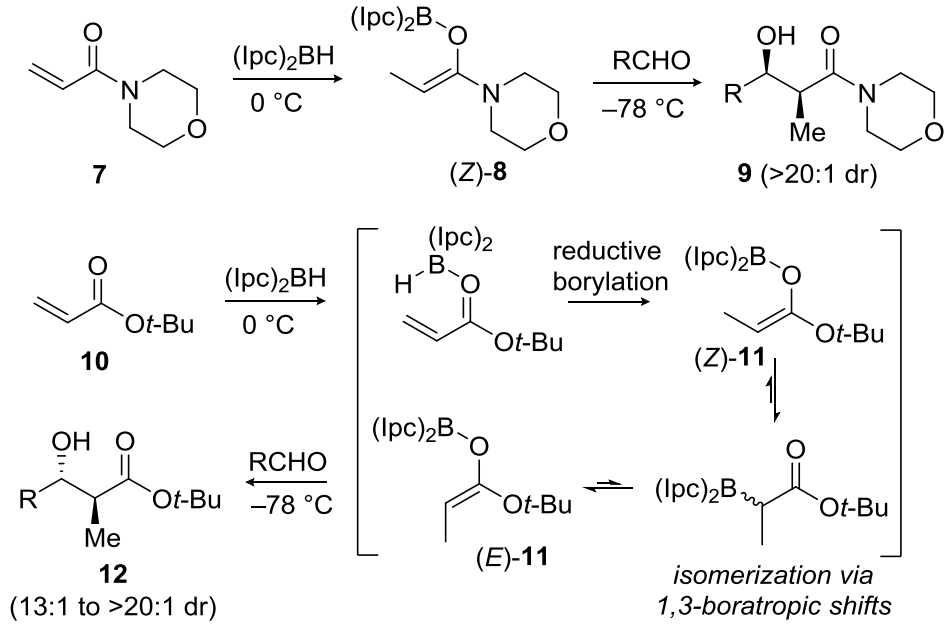


(*E*)-**6** *E*:*Z* = 10:90 (*Z*)-**6**

In sharp contrast to ketone-derived enol borinates, certain ester-derived enol borinates undergo facile isomerization at or below 0 °C via reversible 1,3-boratropic rearrangement. As reported by

Roush *et al.*,[27] isomerization of (*Z*)-**8** to the corresponding (*E*)-enol borinate did not occur, evidently due to 1,3-allylic strain that develops between the morpholine unit and the enolate methyl substituent. Therefore, the reductive aldol reactions of *N*-acryloylmorpholine **7** were highly selective for the *syn*-aldol **9** (Scheme 1-8). Replacing the morpholine amide of **7** with an ester unit as in **10** eliminates this 1,3-interaction and the enol borinate (*Z*)-**11** obtained from 1,4-reduction of acrylate **10** undergoes a reversible 1,3-boratropic shift to afford the presumably more stable and(or) more reactive enolate (*E*)-**11**. Hence, the reductive aldol reactions of **10** resulted in *anti*-aldol products **12** with high diastereoselectivity.

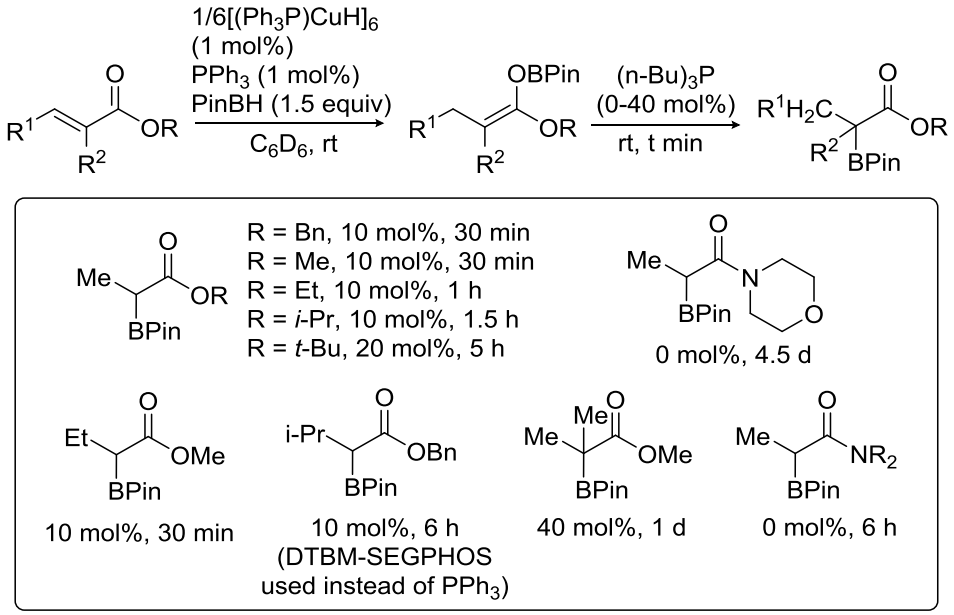
Scheme 1-8. Isomerization of ester-derived enol borinates via 1,3-boratropic shifts.



In addition, ester-derived enol pinacolborates have been reported to be isomerized to α-boryl esters via copper-catalyzed *O*-to-*C* 1,3-boratropic rearrangement in the presence of a catalytic amount of phosphine (Scheme 1-9).[28] Spectroscopic analysis provided evidence supporting that these α-boryl esters are indeed stable even without stabilization by quaternization. It was rationalized that the diminished Lewis acidity of BPin (compared to BR_2) provided less electron donation from the enolate oxygen to the boron center and resulted in less preference for the enol borate isomer. The scope of this *O*-to-*C* 1,3-boratropic rearrangement is quite broad, ranging from primary, secondary, and tertiary esters, as well as α,α-disubstituted and β,β-disubstituted esters. Amides undergo rearrangement more readily than esters, and do not require nucleophilic phosphine to induce the isomerization. However, the generation of α-boryl ketones from enol

borinates of ketones under this protocol were unsuccessful. This can be attributed to the greater resonance delocalization of amides compared to esters and ketones, resulting in stabilization of the carbonyl group and therefore a higher preference for the formation of α-boryl amides and esters over α-boryl ketones.

Scheme 1-9. Preparation of α-boryl esters and amides via copper-catalyzed *O*-to-*C* isomerization.

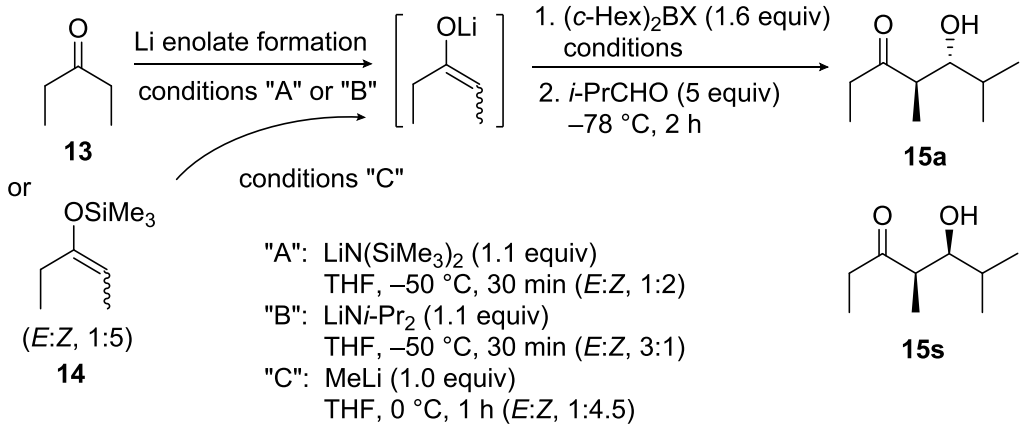


1.3.2 D. Kundu's study

D. Kundu conducted a detailed study[29-31] on the Li and B enolates of 3-pentanone (**13**) to further explore the highly (*E*)-selective phenomenon as previously observed by M. Biniaz. Reaction of the $LiN(SiMe_3)_2$-generated lithium enolate of **13** (*E*:*Z*, 1:2) with $(c\text{-Hex})_2BCl$ followed by addition of *i*-PrCHO under conditions similar to those used by M. Biniaz (cf. Scheme 1-5) afforded a 6:1 mixture of **15a** and **15s**, respectively (Table 1-2, entry 2). Extending the borylation time and(or) increasing the borylation temperature led to almost perfect selectivity toward **15a** (Table 1-2, entries 3, 4). In contrast, borylation of the $LiN(i\text{-Pr})_2$-generated Li enolate (*E*:*Z*, 3:1) under the same conditions produced a 3.2:1 mixture of **15a** and **15s**, respectively, a result that closely reflected the diastereomeric ratio of the parent Li enolate (Table 1-2, entries 5, 6). Interestingly, the high selectivity in favour of the *anti*-adduct **15a** was restored when $HN(SiMe_3)_2$ was added after borylation (Table 1-2, entry 7).[30] Similar borylation of the amine-free Li enolate (*E*:*Z*, 1:5) obtained from trimethylsilyl enol ether **14** produced a 1:4.5 mixture of **15a** and **15s**, consistent with the initial Li enolate geometry (Table 1-2, entries 8, 9). However, the high

selectivity in favour of the *anti*-adduct **15a** was again restored when $HN(SiMe_3)_2$ was added after borylation (entry 10).[31] These observations strongly suggested that an isomerization to the (*E*)-enol borinate of **13** was induced by $HN(SiMe_3)_2$.

Table 1-2. Formation and isomerization of the enol dicyclohexylborinate of 3-pentanone.



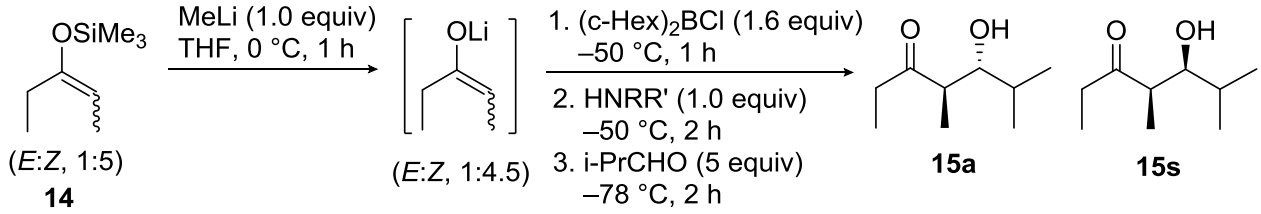
entry	Li enolate conditions[a]	borylation conditions	**15a**:**15s**[b]
1	A	none[c]	1:2
2	A	X = Cl, –78 °C, 2 h	6:1
3	A	X = Cl, –50 °C, 2 h	9:1
4	A	X = Cl, –50 °C, 4 h	>19:1 (86%)[d]
5	B	none[c]	2.9:1
6	B	X = Cl, –50 °C, 4 h	3.2:1 (71%)[d]
7	B	X = Cl, –50 °C, 2 h; then $HN(SiMe_3)_2$ (1.0 equiv), –50 °C, 2 h	>19:1
8	C	none[c]	1:5
9	C	X = Cl, –50 °C, 3 h	1:4.5
10	C	X = Cl, –50 °C, 1 h; then $HN(SiMe_3)_2$ (1.0 equiv), –50 °C, 2 h	>19:1 (89%)[d]

[a] The indicated diastereomer ratios of the Li enolates were determined by ^{1}H NMR of the crude enol ethers obtained by addition of Me_3SiCl/Et_3N to the enolate at –78 °C followed by a non-aqueous work up. [b] Determined by ^{1}H NMR of the crude reaction mixture after work up. [c] Direct addition of *i*-PrCHO at –78 °C followed by work up after 3 min. [d] Isolated yield of **15a**.

Different silyl amines were added following the borylation of the 'amine-free' lithium enolate of **13** to determine whether the silyl ligands were important.[31] Addition of $HN(SiMe_3)_2$, $HNPh(SiMe_3)$, or HN*t*-Bu($SiMe_3$) produced **15a** selectively after aldolization with *i*-PrCHO

(Table 1-3, entries 2 – 4). However, when an *N*-$SiMe_3$ group was lacking, the amine had little effect on isomerization (entries 5, 6). These results suggested that certain *N*-$SiMe_3$ amines catalyse the isomerization of the (*Z*)-enol dicyclohexylborinate of **13** to the (*E*)-isomer.

Table 1-3. Amine-induced isomerization of the enol dicyclohexylborinate of 3-pentanone.



(*E*:*Z*, 1:5)
14

(*E*:*Z*, 1:4.5)

15a

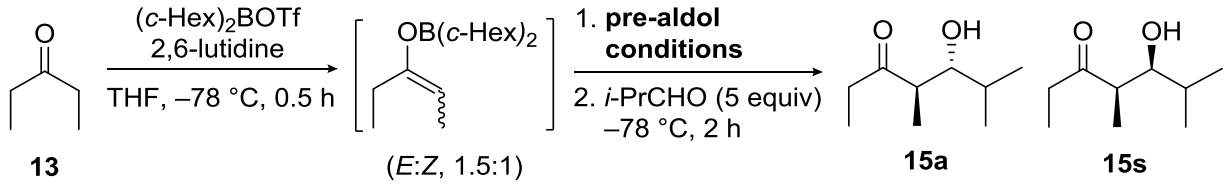
15s

entry	conditions	**15a**:**15s**[a]
1	HNRR' = none	1:4.5
2	HNRR' = $HN(SiMe_3)_2$	>19:1
3	HNRR' = $HNPh(SiMe_3)$	>19:1
4	HNRR' = $HN^tBu(SiMe_3)$	>19:1
5	HNRR' = HNH(*t*-Bu)	1:4.5
6	HNRR' = $HN(SiMe_2Ph)_2$	1:4

[a] Determined by ^1H NMR of the crude reaction mixture after work up.

A study on the enol dicyclohexylborinates generated by 'soft enolization' was also conducted to ascertain whether the process requires starting from the Li enolates.[30] The enol dicyclohexylborinate of **13** was prepared by reaction with (*c*-Hex)$_2$BOTf and 2,6-lutidine at –78 °C for 0.5 h followed by addition of excess *i*-PrCHO to give a 1.5:1 mixture of **15a** and **15s**, respectively (Table 1-4, entry 1). The amount of *anti*-product **15a** was increased to more than 95% by addition of $HN(SiMe_3)_2$ (2.0 equiv) followed after 2 h by addition of excess *i*-PrCHO (entry 3), thus implying that an isomerization of (*Z*)- to (*E*)-enol dicyclohexyl-borinate had occurred and showing that the presence of starting Li enolate was not required.

Table 1-4. Relative reactivity and thermodynamic equilibrium of enol dicyclohexyl-borinate of 3-pentanone.



entry	pre-aldol conditions	**15a**:**15s**[a]
1	none[b]	1.5:1
2	none[b]	2.8:1[c]
3	$HN(SiMe_3)_2$ (2.0 equiv), –50 °C, 2 h	>19:1
4	50 °C, 2 h	6:1
5	50 °C, 4 h	6:1

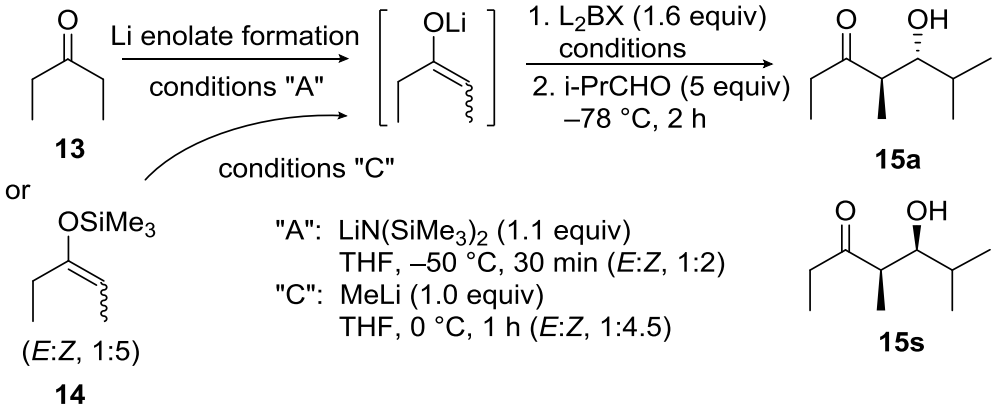
[a] Determined by ^{1}H NMR of the crude reaction mixture after work up. [b] Direct addition of *i*-PrCHO at –78 °C followed by work up after enolate formation. [c] Aldol with 0.2 equiv of *i*-PrCHO.

The relative reactivity of the (*E*)- and (*Z*)-enol dicyclohexylborinates of **13** toward *i*-PrCHO was measured to assess the potential dependence of the observed selectivities on a preferential reaction of (*E*)-enol borinates in an equilibrating *E*:*Z* mixture.[30] The result obtained after treatment of the enol borinates of **13** generated by 'soft enolization' with a deficient amount of *i*-PrCHO (0.2 equiv) (Table 1-4, entry 2) implied that the (*E*)-enol dicyclohexylborinate of **13** was ca. 1.9 times more reactive than the (*Z*)-isomer. The equilibrium ratio of (*Z*)- and (*E*)-enol dicyclohexylborinate of **13** was measured as 1:6 using Evan's protocol[12] (entries 4, 5). The much greater ratio favouring the (*E*)-enol borinate under conditions at –50 °C implies a more complex underlying process than just equilibration of 'free' enol borinates.

The effects of the leaving group and the steric bulk of the ligands of the borylating reagents on the isomerization process were studied using dicyclohexylboron triflate (c-Hex_2BOTf),[30] 9-borabicyclo[3.3.1non-9-yl triflate (9-BBNOTf),[29] and dibutylboron triflate (Bu_2BOTf)[30] (Table 1-5). Similar results were obtained using (c-Hex)$_2$BOTf in place of (c-Hex)$_2$BCl (entries 1, 2), suggesting that the leaving group in the borylating reagent has a minimal effect on the isomerization process. Borylation of $LiN(SiMe_3)_2$-generated Li enolate of **13** (*E*:*Z*, 1:2) with 9-BBNOTf at –50 °C for 2 h followed by aldolization with *i*-PrCHO gave a 4.5:1 mixture of **15a** and **15s**, respectively (entry 3). In a similar way, borylation of $LiN(SiMe_3)_2$-generated Li enolate of **13** (*E*:*Z*, 1:2) with Bu_2BOTf at –50 °C for 2 h followed by aldolization with *i*-PrCHO gave a

8:1 mixture of **15a** and **15s**, respectively (entry 4). These results suggest that the bulkiness of the boron ligands could influence the stereoselectivity. In addition, the effect of the amount of $HN(SiMe_3)_2$ present during the isomerization process after borylation of the 'amine-free' Li enolate of **13** was explored, which showed that higher selectivities toward **15a** were obtained with increasing stoichiometry of $HN(SiMe_3)_2$ (Table 1-5, entries 5–10).[30] The dependence of reaction selectivity on the bulkiness of boron ligands and the amount of $HN(SiMe_3)_2$ suggested the involvement of an enolborinate-amine complex in the isomerization.

Table 1-5. Formation and isomerization of various enol borinates of 3-pentanone.

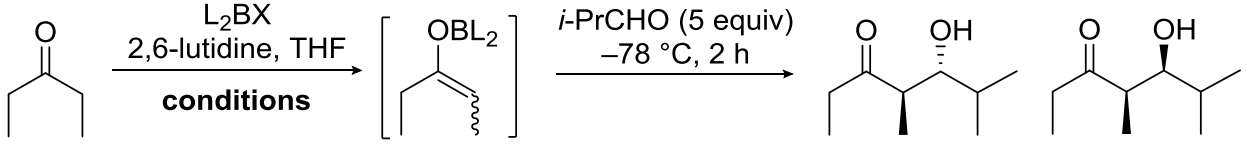


entry	Li enolate conditions[a]	borylation conditions	**15a**:**15s**[b]
1	A	L = *c*-Hex, X = Cl, –50 °C, 2 h	9:1
2	A	L = *c*-Hex, X = OTf, –50 °C, 2 h	8:1
3	A	L_2B-X = 9-BBN-OTf; –50 °C, 2 h	4.5:1
4	A	L = Bu, X = OTf; –50 °C, 2 h	8:1
5	C	X = Cl, –50 °C, 1 h; then $HN(SiMe_3)_2$ (0.5 equiv), –50 °C, 2 h	12:1
6	C	X = Cl, –50 °C, 1 h; then $HN(SiMe_3)_2$ (1.0 equiv), –50 °C, 2 h	>19:1
7	C	L_2B-X = 9-BBN-OTf; –50 °C, 1 h; then $HN(SiMe_3)_2$ (0.5 equiv), 0 °C, 15 min	2.5:1
8	C	L_2B-X = 9-BBN-OTf; –50 °C, 1 h; then $HN(SiMe_3)_2$ (2.0 equiv), 0 °C, 15 min	5.5:1
9	C	L = Bu, X = OTf; –50 °C, 1 h; then $HN(SiMe_3)_2$ (0.4 equiv), 0 °C, 15 min	4.5:1
10	C	L = Bu, X = OTf; –50 °C, 1 h; then $HN(SiMe_3)_2$ (2.0 equiv), 0 °C, 15 min	9:1

[a] The indicated diastereomer ratios of the Li enolates were determined by ^{1}H NMR of the crude enol ethers obtained by addition of Me_3SiCl/Et_3N to the enolate at –78 °C followed by a non-aqueous work up. [b] Determined by ^{1}H NMR of the crude reaction mixture after work up.

The relative reactivities toward *i*-PrCHO and equilibrium ratio of the (*E*)- and (*Z*)-isomers of various enol borinates of **13** were measured (Table 1-6).[30] Simple consideration of the relative reactivities of the 9-BBN-OTf generated-enol borinate diastereoisomers (*E*:*Z*, 1.7:1; cf. Table 1-6, entries 1, 2) and the equilibrium ratio (*E*:*Z*, 1:2.2 at 50 °C; Table 1-6, entry 3) of the enol borinates predicts that the ratio of products after aldol reaction with excess *i*-PrCHO at –78 °C should favour *syn* isomer, even if the enol borinates were rapidly equilibrating. However, reaction of $LiN(SiMe_3)_2$-generated Li enolates of **13** with 9-BBN-OTf followed by addition of excess *i*-PrCHO gave *anti*-product predominantly (**15a**:**15s**, 4.5:1; cf. Table 1-5, entry 3). Similarly, reaction of $LiN(SiMe_3)_2$-generated Li enolates of **13** with Bu_2BOTf followed by addition of excess *i*-PrCHO gave *anti*-product predominantly (**15a**:**15s**, 8:1; cf. Table 1-5, entry 4), being inconsistent with the relative reactivites (*E*:*Z*, 1.8:1; cf. Table 1-6, entries 4, 5) and the equilibrium ratio (*E*:*Z*, 1:1 at 50 °C; Table 1-6, entry 6) of the corresponding enol borinate diastereomers. These inconsistencies between the predicted and observed aldol stereoselectivities further supported that the isomerization should not be occurring on 'free' enol borinates but on an enolborinate-amine complex.

Table 1-6. Relative reactivities toward *i*-PrCHO and thermodynamic equilibria of various enol borinates of 3-pentanone.



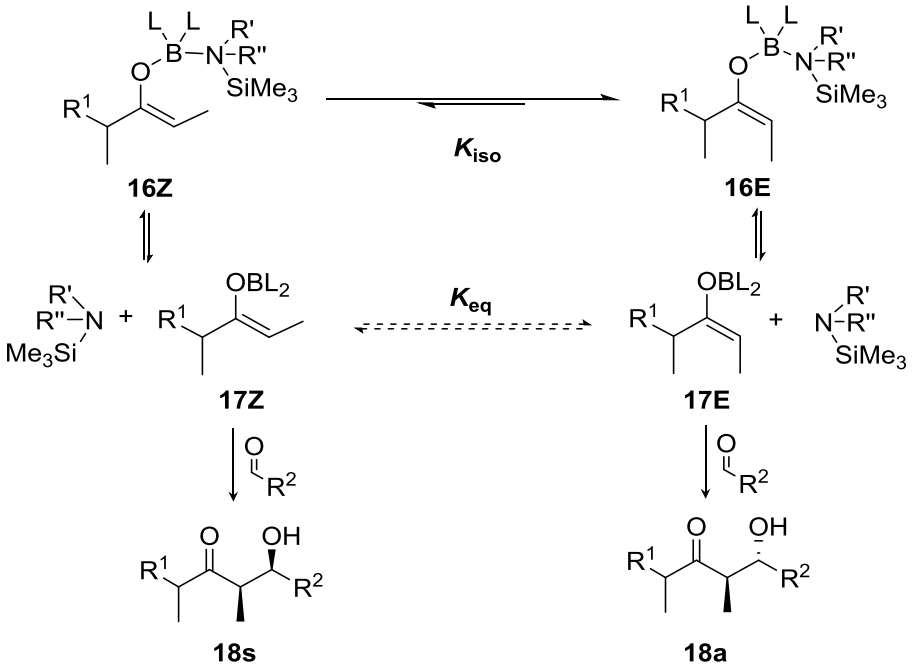
13 **15a** **15s**

entry	borylation conditions	**15a**:**15s**[a]
1	L_2B-X = 9-BBN-OTf; –78 °C, 0.5 h	1:5
2	L_2B-X = 9-BBN-OTf; –78 °C, 0.5 h	1:3[b]
3	L_2B-X = 9-BBN-OTf; –78 °C, 0.5 h then 50 °C, 2 h	1:2.2
4	L = Bu, X = OTf; –78 °C, 0.5 h	1:1.5
5	L = Bu, X = OTf; –78 °C, 0.5 h	1.2:1[b]
6	L = Bu, X = OTf; –78 °C, 0.5 h then 50 °C, 2 h	1:1

[a] Determined by ^{1}H NMR of the crude reaction mixture after work up. [b] Aldol with 0.2 equiv. of *i*-PrCHO.

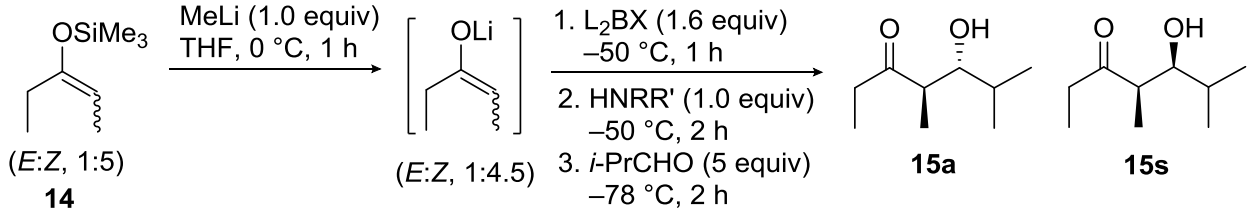
With these three lines of evidence supporting the involvement of *N*-$SiMe_3$ amine – enol borinate complexes as discussed above, D. Kundu proposed a mechanism to explain the obtained selectivities (Scheme 1-10).[31] In this hypothesis, isomerization of the boron enolates proceeds over three reversible steps: formations of complexes **16Z** and **16E** and their isomerization. Assuming equilibrium has been achieved prior to addition of aldehyde, the ratio of aldol products will depend on the equilibrium ratio and relative reactivity of **17**, the equilibrium ratio and the amount of complexes **16**, and the relative rates of aldol reaction of **17** versus isomerization of **16**. It was assumed that the aldol reaction is faster than isomerization when excess *i*-PrCHO is added to the enol borinates at –78 °C. Under these conditions, kinetic trapping dictates that the ratio **15a** (= **18a**, R^1 = H, R^2 = *i*-Pr) and **15s** (= **18s**, R^1 = H, R^2 = *i*-Pr) should reflect the ratio of (**16E**+**17E**) and (**16Z**+**17Z**), respectively. Because of the increased steric bulk associated with the additional boron ligand in **16** compared to **17**, the isomerization equilibrium K_{iso} is expected to have a greater proportion of the (*E*)-isomer than K_{eq}. Consequently, aldol stereoselectivities can be correlated to the amount of **16** present. Consistent with this analysis, the aldol diastereoselectivity (**15a**:**15s**) was found to vary with the amount of added HNR'$SiMe_3$ (changes **16**) (cf. Table 1-5, entries 5–10).

Scheme 1-10. Proposed mechanism for *N*-$SiMe_3$ induced isomerization of enol borinates by Kundu.



The involvement of the amine-enol borinate complexes in the proposed mechanism as shown in Scheme 1-10 was further supported by the changes in diastereoselectivity of aldol reaction with variations in the identity of HNR'$(SiMe)_3$ (Table 1-7).[30] Although aldol diastereoselectivities after treatment of enol borinates with $HN(SiMe_3)_2$ or $HNPh(SiMe_3)$ were similar (**15a**:**15s**, 5:1) (Table 1-7, entries 1, 2), the use of HN*t*-Bu$(SiMe_3)$ afforded much higher selectivity (**15a**:**15s**, >19:1) (entries 3, 5). This dependence on the identity of HR'$NSiMe_3$ presumably relates to changes in K_{iso} resulting from changes in the steric bulk of the R' group (Scheme 1-10).

Table 1-7. Changes in aldol diastereoselectivities with variations in the identity of $HNR(SiMe)_3$.



entry	conditions	**15a**:**15s**[a]
1	L_2B-X = 9-BBN-OTf; –50 °C, 1 h; then $HN(SiMe_3)_2$ (1.0 equiv), 0 °C, 15 min	5:1

2	L_2B-X = 9-BBN-OTf; –50 °C, 1 h; then HNPh($SiMe_3$) (1.0 equiv), 0 °C, 15 min	5:1
3	L_2B-X = 9-BBN-OTf; –50 °C, 1 h; then HN*t*-Bu($SiMe_3$) (1.0 equiv), 0 °C, 15 min	>19:1
4	L = Bu, X = OTf; –50 °C, 1 h; then HN($SiMe_3$)$_2$ (1.0 equiv), 0 °C, 15 min	9:1
5	L = Bu, X = OTf; –50 °C, 1 h; then HN*t*-Bu($SiMe_3$) (1.0 equiv), 0 °C, 15 min	>19:1

[a] Determined by ^{1}H NMR of the crude reaction mixture after work up.

The above results strongly support the involvement of the *N*-$SiMe_3$ – enol borinate complexes **16** as a key intermediate in the isomerization process. Moreover, the reversible 1,3-boratropic rearrangement of **17**, as proposed for the ester-derived enol borinates,[27] seems unlikely and does not explain the observed catalysis by *N*-$SiMe_3$ amines. Two possible pathways (via intermediate **A** or **B**) for isomerization of **16** were proposed (Scheme 1-11).[31] Isomerization of **16** by a reversible 1,5-hydrogen migration mechanism via intermediate **A** was ruled out because reaction of boron enolate of **13** with DN($SiMe_3$)$_2$ followed by addition of *i*-PrCHO gave **15a** selectively but with <10% deuterium incorporation (Table 1-8, entry 1) and the use of Me_2NSiMe_3 (where 1,5-H transfer was not possible) was as effective as HN($SiMe_3$)$_2$ in mediating the presumed boron enolate isomerization (entries 2 and 3).[31] Thus, a plausible mechanism for isomerization that accounts for the requirement of an *N*-$SiMe_3$ amine involves a 1,5-silyl transfer via intermediate **B** (Scheme 1-11).

Scheme 1-11. Mechanism for the isomerization of *N*-trimethylsilyl amine-enol borinate complexes proposed by D. Kundu.

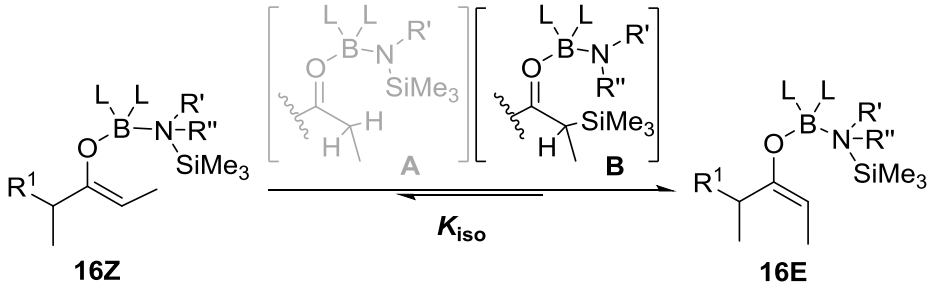
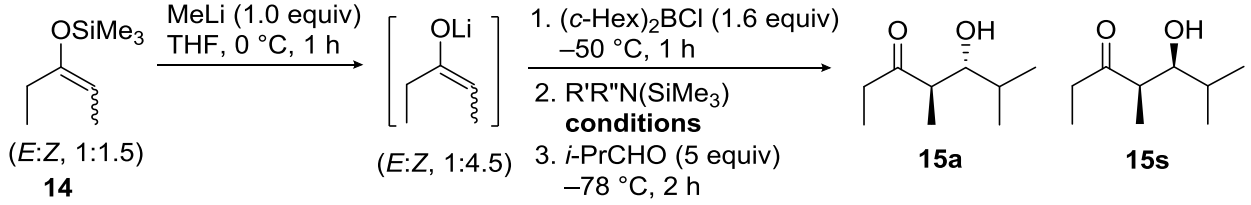


Table 1-8. The effect of *N*-D and tertiary *N*-$SiMe_3$ amines on enol borinate isomerization.



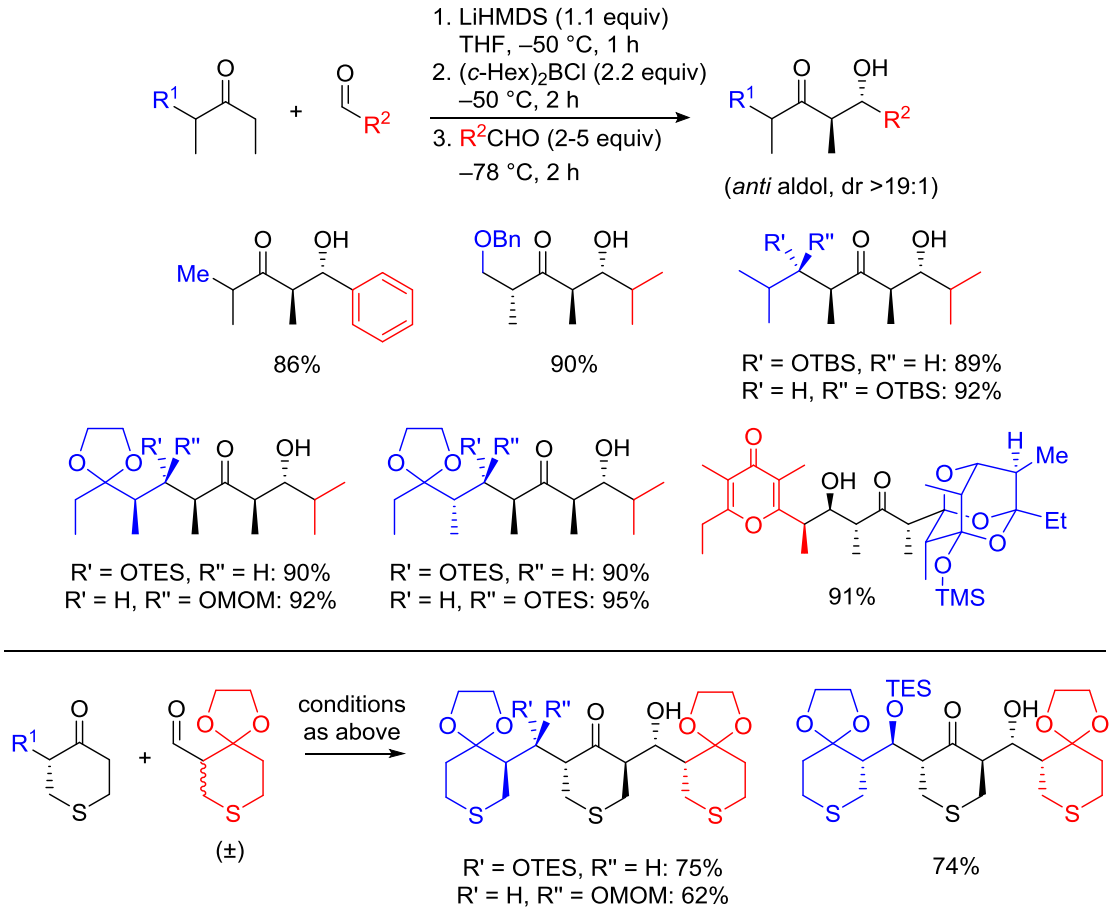
(*E*:*Z*, 1:1.5) **14** (*E*:*Z*, 1:4.5) **15a** **15s**

entry	conditions	**15a**:**15s**[a]
1	$DN(SiMe_3)_2$ (4.0 equiv), –50 °C, 2 h	>19:1[b]
2	$HN(SiMe_3)_2$ (1.0 equiv), –50 °C, 2 h	>19:1
3	Me_2NSiMe_3 (1.0 equiv), –50 °C, 2 h	>19:1

[a] Determined by ^{1}H NMR of the crude reaction mixture after work up. [b] <10% deuterium incorporation in **15a**.

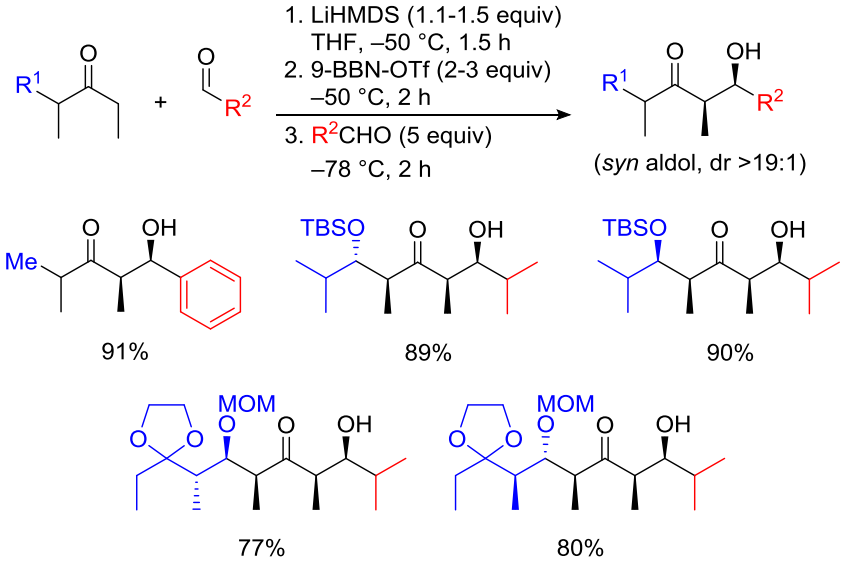
The application of optimized lithiation-borylation-isomerization conditions to a series of ethyl ketones of increasing structural and stereochemical complexity was reported by D. Kundu.[31] In each case, *anti*-aldol adducts were obtained with excellent diastereoselectivity and yield (Scheme 1-12). The methodology was also reported to be applicable to selected cyclic ketones which were previously reported to give low to moderate yields of aldol adducts using 'soft enolization' to prepare the corresponding enol borinates.[32] In these cases, isomerization of enol borinates was not operative because only the (*E*)-enol borinate is possible; however, the yields obtained from the lithiation/borylation method followed by aldol reaction were markedly improved compared to those obtained using a 'soft enolization' approach.

Scheme 1-12. Substrate scope for the lithiation-borylation-isomerization route to (*E*)-enol borinates according to D. Kundu.



A simple method for stereoselective preparation of (*Z*)-enol borinates was also reported, which emerged from the observations that $HN(SiMe_2Ph)_2$ was ineffective as a catalyst for enol borinate isomerization[31] (cf. Table 1-3, entry 6) while $LiN(SiMe_2Ph)_2$ is an excellent reagent[33] for preparation of Li (*Z*)-enolates from ethyl ketones. Several ketones were subjected to aldol reactions following a protocol involving reaction with $LiN(SiMe_2Ph)_2$ to form the Li (*Z*)-enolate, addition of 9-BBN-OTf to generate the corresponding (*Z*)-enol borinate, and then addition of aldehyde (Scheme 1-13). In each case, good yields of *syn* aldol adducts with excellent stereoselectivities were reported.

Scheme 1-13. Substrate scope for the lithiation-borylation-isomerization route to (*Z*)-enol borinates according to D. Kundu.



In summary, the results reported by D. Kundu suggested that:

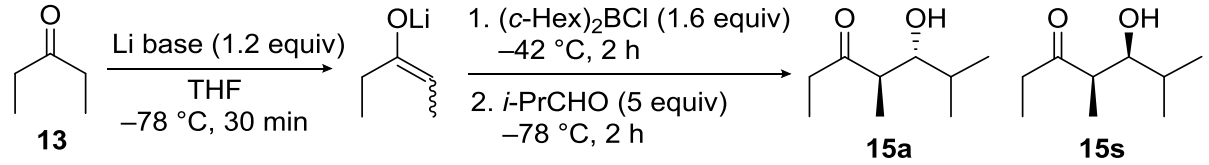
- (*E*)-enol borinates are ca. 2 times more reactive than (*Z*)-enol borinates toward *i*-PrCHO.
- Borylation of $LiN(SiMe_3)_2$-generated Li enolates gives (*E*)-enol borinates with high stereoselectivity.
- The (*E*)-enol borinates result from $HN(SiMe_3)_2$ (or more generally HRN-$SiMe_3$) mediated isomerization of enol borinates.
- The stereoselectivity of the isomerization depends on the stoichiometry of the $HRNSiMe_3$ reagent and the identity of the "R" group.
- The isomerization mechanism involves isomerization of *N*-$SiMe_3$ amine – boron enolate complexes via an unusual 1,5-silyl migration.
- Borylation of $LiN(SiPhMe_2)_2$-generated Li (*Z*)-enolates gives (*Z*)-enol borinates with high stereoselectivity because isomerization does not occur under these conditions.

2 RESULTS AND DISCUSSION

2.1 Project objective

When repeating the borylation of the LiN(*i*-Pr)$_2$-generated Li enolate of **13** (*E*:*Z*, 75:25) according to Kundu's report, I obtained only *anti* product **15a** after aldolization with *i*-PrCHO (Table 2-1, entry 1). This result was inconsistent with the ratio reported by Kundu (**15a**:**15s** = 3.2:1, cf. Table 1-2, entry 6).[30] Repeating the borylation of the LiN(SiMe$_3$)$_2$-generated lithium enolate of **13** followed by addition of *i*-PrCHO also gave **15a** exclusively (Table 2-1, entry 2), similar to Kundu's report (cf. Table 1-2, entries 3 and 4).[29] It is interesting that high *anti* selectivity was also observed using LiN(SiMe$_2$Ph)$_2$ to generate the lithium enolate (Table 2-1, entry 3), which was previously claimed by Kundu to have little effect[31] on borylation/isomerization toward (*E*)-enol borinate (cf. Table 1-3, entry 6).

Table 2-1. Selective formation of **15a** via borylation of lithium enolate followed by aldol reaction with *i*-PrCHO.[a]

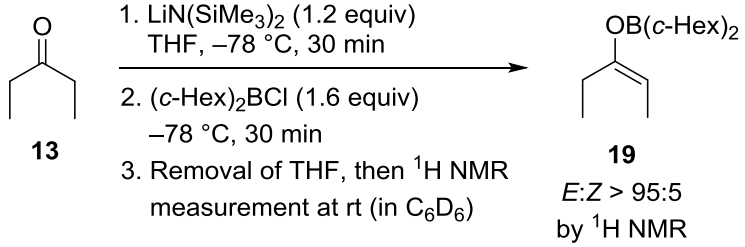


entry	Li amide base	Li enolate *E*:*Z*[b]	**15a**:**15s**[c]	Kundu's report[d] **15a**:**15s**
1	LDA	75:25	>95:5	3.2:1 (76:24)
2	LiHMDS	34:66	>95:5	>19:1 (>95:5)
3	LiN(SiMe$_2$Ph)$_2$	0:100	>95:5	N/A

[a] Reaction conditions: Enolate formation by addition of **13** (0.95 M in THF) to Li amide base (0.20 M in THF) at –78 °C. Borylation by addition of (*c*-Hex)$_2$BCl (1.6 equiv, 1.0 M in hexane) at –78 °C and stirring at –42 °C, and aldolization by addition of *i*-PrCHO (5.0 equiv) at –78 °C. In all cases, the yield (by ^{1}H NMR) of the aldol products **15a** and **15s** was within the range of 92–97% by comparison of crude aldol with trichloroethylene as the internal standard. See Experimental Section for detailed procedure. [b] Determined by ^{1}H NMR of the crude enol ethers obtained by addition of Me$_3$SiCl/Et$_3$N (5.0 equiv) to the enolate at –78 °C. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] cf. Table 1-2.

Direct ^{1}H NMR measurement of the enolate mixture after borylation predominantly showed the vinyl proton of the (*E*)-enol dicyclohexylborinate **19**, indicating that the observed *anti*-product **15a** was likely to result from aldol reaction of the (*E*)-enol borinate (Scheme 2-1).

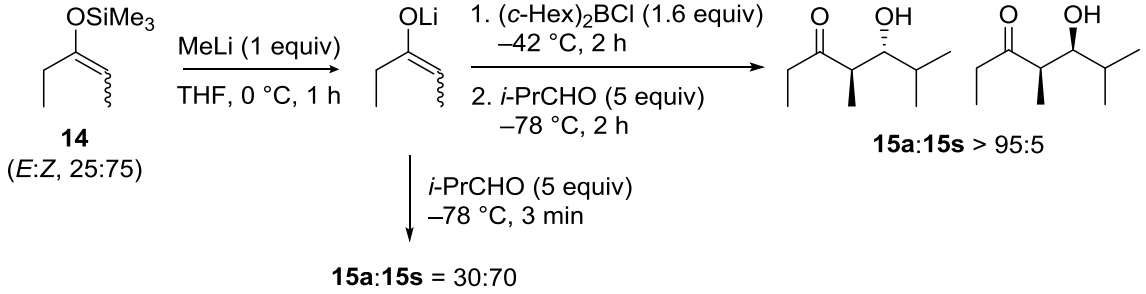
Scheme 2-1.[a] Formation of (*E*)-enol borinate confirmed by direct ^{1}H NMR measurement.



[a] Reaction conditions: Enolate formation by addition of **13** (0.95 M in THF) to LiN(SiMe$_3$)$_2$ (0.20 M in THF) at –78 °C. Borylation by addition of (*c*-Hex)$_2$BCl (1.6 equiv, 1.0 M in hexane) at –78 °C, followed by removal of THF under vacuum and addition of C_6D_6 for direct ^{1}H NMR measurement. A controlled experiment was done in parallel with identical enolization and borylation conditions, and aldolization with *i*-PrCHO (5.0 equiv) at –78 °C was performed after borylation, giving *anti*:*syn* ratio close to the measured ratio of enol borinate.

Kundu concluded that the presence of an *N*-SiMe$_3$ amine was required to form the observed (*E*)-enol borinate from borylation of a lithium (*Z*)-enolate.[31] My observation of exclusive formation of **15a** from borylation of the LiN(*i*-Pr)$_2$-generated lithium enolate of **13** is inconsistent with Kundu's conclusion. The role of amines was further tested by borylation of the 'amine-free' Li enolate (Scheme 2-2). The nearly exclusive formation of **15a** was again inconsistent with the result previously reported by Kundu[31] (**15a**:**15s** = 1:4.5, cf. Table 1-2, entry 9).

Scheme 2-2.[a] Borylation of 'amine-free' Li enolates from silyl enol ether **14**.



[a] Reaction conditions: Enolate formation by addition of MeLi (1.65 M in Et_2O) to **14** (0.20 M in THF) and stirring at 0 °C for 1 h. Borylation by addition of (*c*-Hex)$_2$BCl (1.6 equiv, 1.0 M in hexane) at –78 °C and stirring at –42 °C. Aldolization by addition of *i*-PrCHO (5.0 equiv) at –78 °C.

Because the key experiments reported by Kundu were not reproducible by me, the validity of those results was questionable. Hence, the objective of this project was to re-investigate the origin of this highly selective formation of the (*E*)-enol borinates and evaluate the scope and limitations of the method. The project was designed based on two possible hypotheses for the formation of an (*E*)-enol borinate by borylation of a lithium (*Z*)-enolate: (1) *O*-borylation generating the (*Z*)-enol

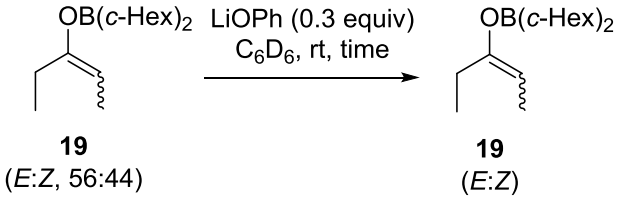
borinate followed by isomerization to the (*E*)-enol borinate, or (2) *C*-borylation generating an unstable α-boryl ketone that stereoselectively rearranges to afford the (*E*)-enol borinate.

2.2 Mechanistic study

2.2.1 Thermodynamic equilibrium of enol borinates

The equilibrium ratio of (*E*)- and (*Z*)-enol dicyclohexylborinates **19** of 3-pentanone was evaluated by isomerization according to Masamune's protocol, using LiOPh at room temperature in benzene.[25] The results showed that enol borinate **19** can be isomerized under these conditions, which led to an equilibrium ratio of 93:7 in favor of (*Z*)-enol borinate (Table 2-2).

Table 2-2. Isomerization of enol borinate **19** mediated by LiOPh in benzene.[a]

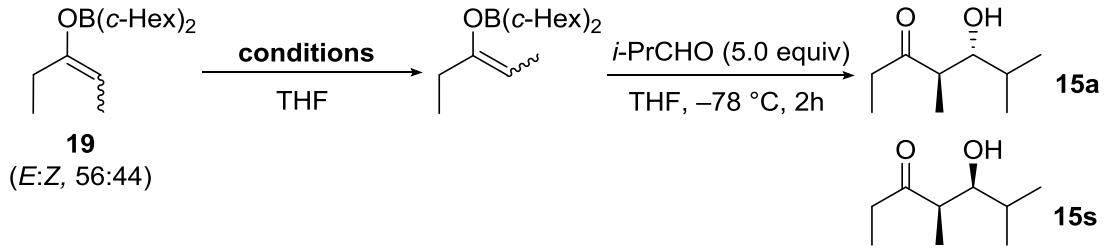


entry	time	(*E*:*Z*)-**19**[b]
1	2 h	29:71
2	4 h	17:83
3	11 h	7:93
4	18 h	7:93

[a] Reaction conditions: Addition of LiOPh (0.3 equiv, 1.0 M in C_6D_6) to the preformed enol borinates (0.5 M in C_6D_6) in NMR tube at rt under Ar. Direct ^{1}H NMR was run after letting the mixture sit at rt for indicated time. See Experimental Section for detailed procedure. [b] Determined directly by ^{1}H NMR of the reaction mixture.

The consistency between the ratio of the aldol adducts **15a**:**15s** resulting after addition of *i*-PrCHO to **19** and the geometry of the parent enol borinates provided a useful indirect measurement of the *E:Z* ratio of enol borinates (Table 2-3, entry 1). Thus, LiOPh-mediated isomerization of enol dicyclohexylborinate **19** was evaluated in THF. The results showed that the isomerization occurred at similar rates in benzene and THF (Table 2-2, entries 1, 2, 4 and Table 2-3, entries 2-4). The final equilibrium ratios observed in benzene and THF were also consistent with the computed equilibrium ratio for the 'free' enol dicyclohexylborinates, which is *E*:*Z* = 8:92 [DFT: m06-2x/6-31G+(d,p) with THF solvation (Polarizable Continuum Model)].[34] The results obtained experimentally and computationally were again inconsistent with the equilibrium ratio reported by Kundu[30] (*E*:*Z*, 6:1; cf. Table 1-4, entries 4 and 5).

Table 2-3. Isomerization of **19** mediated by LiOPh in THF.[a]

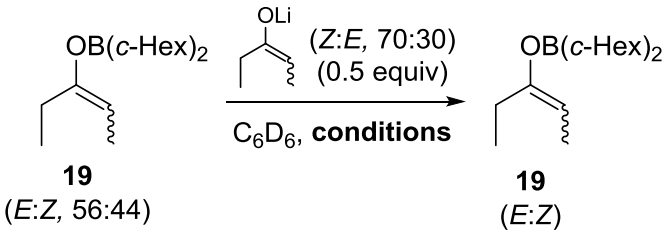


entry	conditions	**15a**:**15s**[b]
1	None	56:44
2	LiOPh (0.3 equiv), rt, 2 h	24:76
3	LiOPh (0.3 equiv), rt, 4 h	18:82
4	LiOPh (0.3 equiv), rt, 18 h	7:93

[a] Reaction conditions: Isomerization by addition of LiOPh (0.3 equiv, 0.5 M in THF/Hexane) to **19** (*Z*:*E*, 44:56*;* 0.4 M in THF) at rt under Ar, followed by addition of *i*-PrCHO after stirring at rt for indicated time. See Experimental Section for detailed procedure. [b] Determined directly by ^{1}H NMR of the crude aldol product after quenching and workup.

Interestingly, the equilibration of enol dicyclohexylborinate **19** can also be achieved by using the lithium enolate as the catalyst (Table 2-4, entry 1–3). Comparing the results obtained with the two catalysts, isomerization was much faster with the lithium enolate than lithium phenolate at room temperature. Isomerization catalyzed by the lithium enolate was negligible at –42 °C (Table 2-4, entry 4).

Table 2-4. Isomerization of **19** mediated by Li enolate in benzene.

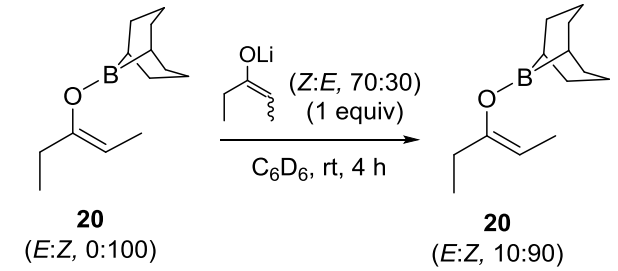


entry	conditions[a]	(*E*:Z)-**19**[b]
1	rt, 20 min	35:65
2	rt, 2 h	7:93
3	rt, 16 h	7:93
4	–42 °C, 1 h[c]	56:44

[a] Reaction conditions: Addition of Li enolates (*Z*:*E* = 70:30; 0.5 equiv, 1.0 M in C_6D_6) to **19** (0.5 M in C_6D_6) in NMR tube at rt under Ar. Direct ^{1}H NMR was run at indicated temperature after letting the mixture sit for indicated time. See Experimental Section for detailed procedure. [b] Determined directly by ^{1}H NMR of the reaction mixture. [c] Toluene-d_8 was used instead of C_6D_6.

Evans *et al.* reported the equilibrium ratio of enol dibutylborinates of 3-pentanone also favored the (*Z*)-isomer (*E*:*Z*, 14:86).[12] The change in boron ligand presumably resulted in a slightly different equilibrium ratio. With interest in the effect of boron ligands on the equilibration of enol borinates, the isomerization of 9-BBN-OTf-generated enol borinate **20** was also evaluated, which showed equilibrium at *E*:*Z* = 10:90 (Scheme 2-3).

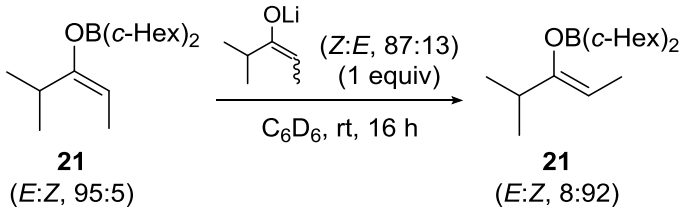
Scheme 2-3.[a] Thermodynamic equilibrium of enol borinate **20**.



[a] Reaction conditions: Addition of Li enolate (*Z*:*E* = 70:30; 1.0 equiv, 1.0 M in C_6D_6) to the preformed enol borinate **20** (*E*:*Z*, 0:100; 0.5 M in C_6D_6) in NMR tube at rt under Ar. Isomerization of **20** was monitored by ^{1}H NMR at rt. See Experimental Section for detailed procedure.

The (*Z*)-enol borinate was also the thermodynamically favored isomer in the case of enol dicyclohexylborinate **21** of 2-methyl-3-pentanone (Scheme 2-4). These results are consistent with literature reports suggesting that (*Z*)-enol borinates are the more thermodynamically favored product.[12, 25, 26]

Scheme 2-4.[a] Thermodynamic equilibrium of enol dicyclohexylborinate **21**



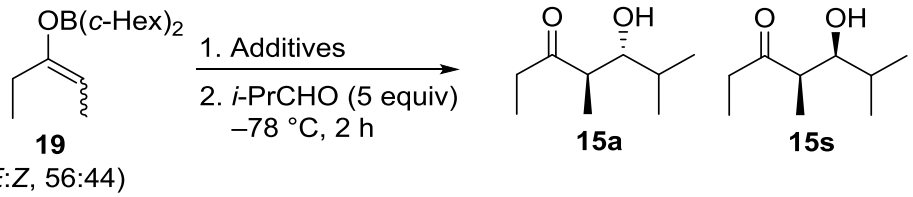
[a] Reaction conditions: Addition of Li enolate (*Z*:*E*, 87:13; 1.0 equiv, 1.0 M in C_6D_6) to the preformed enol borinate **21** (*E*:*Z*, 95:5; 0.5 M in C_6D_6) in NMR tube at rt under Ar. Isomerization of **21** was monitored by ^{1}H NMR. See Experimental Section for detailed procedure.

2.2.2 Testing for potential isomerization under borylation conditions

To evaluate the potential for isomerization of enol borinates under lithiation/borylation conditions, preformed enol borinate **19** was treated with different plausible additives directly involved in the borylation step: secondary amines, (*c*-Hex)$_2$BCl, and LiCl. Amines, both silylated and non-silylated, were initially screened but showed no evidence of isomerization of the enol

borinates under reaction conditions comparable with those used for the borylation of Li enolates, confirming that the amines do not play any significant role in isomerization of enol borinates (Table 2-5, entries 2, 3). These observations are in stark contrast with the previous report by Kundu suggesting that various trimethylsilyl amines catalyzed the isomerization of enol borinates[31] (cf. Table 1-3, entries 2–4). Using (*c*-Hex)$_2$BCl as an additive did not cause any change in the diastereomer ratio of **19** (Table 2-5, entries 4, 5), implying that the excess 0.6 equiv. of (*c*-Hex)$_2$BCl in the borylation step did not induce the isomerization of enol borinates. The by-product of the borylation reaction, LiCl, was also added to the enol borinate but showed no effect on the enol borinate geometry (Table 2-5, entry 7). All chosen additives, either separately (Table 2-5, entries 2–6) or in a combination (entries 7–11), did not show any sign of isomerization of the 'free' enol borinates under conditions similar to those used for borylation of lithium enolates.

Table 2-5. Screening of additives related to borylation conditions.



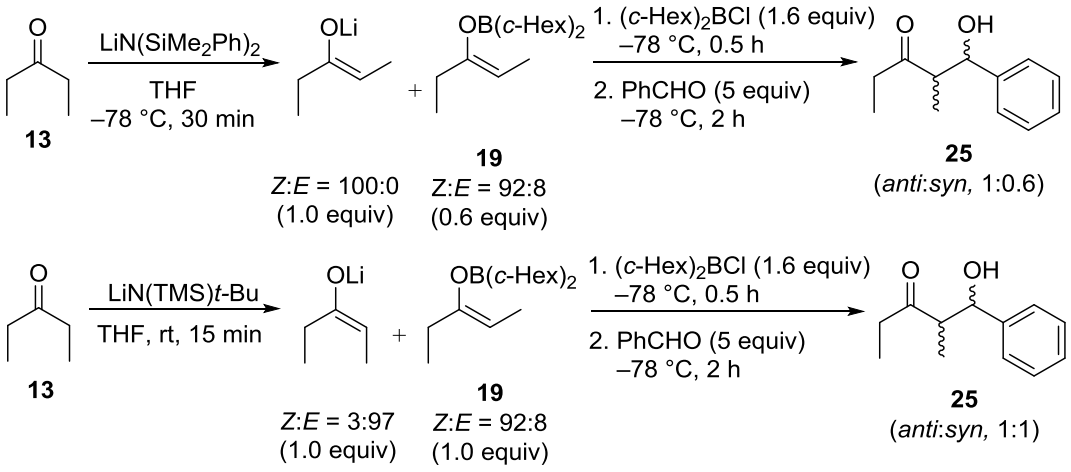
19 (*E*:*Z*, 56:44) **15a** **15s**

entry	additives[a]	conditions	**15a**:**15s**[b]
1	None	–42 °C, 2 h	56:44
2	HMDS	–42 °C, 2 h	56:44
3	DIPA	–42 °C, 2 h	56:44
4	(*c*-Hex)$_2$BCl	–78 °C, 1 h	57:43
5	(*c*-Hex)$_2$BCl	–78 °C, 2 h	57:43
6	LiCl	–78 °C, 1 h	56:44
7	LiCl + (*c*-Hex)$_2$BCl	–78 °C, 1 h	57:43
8	LiCl + HMDS	–78 °C, 1 h	55:45
9	LiCl + HMDS + (*c*-Hex)$_2$BCl	–78 °C, 1 h	56:44
10	LiCl + HMDS + (*c*-Hex)$_2$BCl	–42 °C, 2 h	56:44
11	LiCl + HMDS + (*c*-Hex)$_2$BCl	–42 °C, 8 h	56:44

[a] Reaction conditions: Addition of additives (1.0 equiv, 'neat' in cases of the amines, or as solution in THF/hexane) to **19** (0.20 M in THF) at –42 °C, and after indicated time, addition of *i*-PrCHO (5.0 equiv) at –78 °C followed by quench and workup after stirring for 2 h. See Experimental Section for detailed procedure. [b] Determined by ^{1}H NMR of the crude reaction mixture.

Mixtures of preformed (*Z*)-enol borinate **19** and each isomer of the lithium enolate from **13** were prepared with known ratios and then subjected to borylation (Scheme 2-5). With both lithium (*E*)- and (*Z*)-enolates, the final *anti*:*syn* ratio of **25**, and thus the *E:Z* enol borinate ratio prior to aldolization, was equal to the initial ratio of the preformed lithium enolates to (*Z*)-enol borinate. These observations suggested that the Li enolates (both *E* and *Z*) were converted to (*E*)-enol borinates, and that the preformed (*Z*)-enol borinate remained unchanged under the borylation conditions.

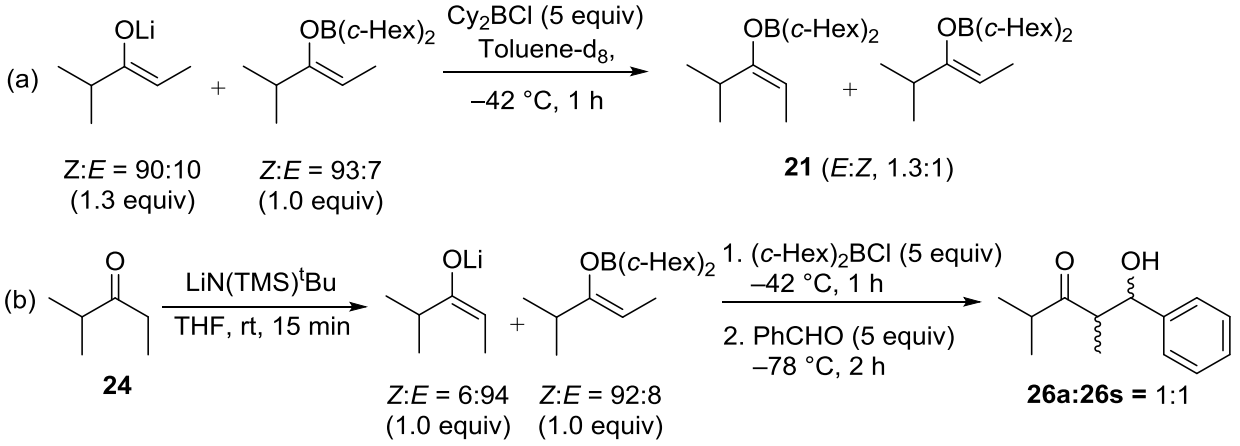
Scheme 2-5.[a] Borylation of Li (*Z*)- and (*E*)-enolates of **13** in presence of (*Z*)-**19**.



[a] Reaction conditions: Li (*E*)- or (*Z*)-enolate formation by addition of **13** (0.95 M in THF) to the corresponding Li amide base (0.20 M in THF). Addition of preformed (*Z*)-**19** (0.5 M in C_6H_6) at –78 °C followed by (*c*-Hex)$_2$BCl (1.6 equiv, 1.0 M in hexane), and aldolization with PhCHO (5.0 equiv) at –78 °C. In all cases, the yield (by ^{1}H NMR) of the aldol products was within the range of 95-99% by comparison of crude aldol product with trichloroethylene as the internal standard. See Experimental Section for detailed procedure.

An analogous approach was applied to examine the isomerization of the (*Z*)-enol borinate **21** of 2-methyl-3-pentanone **24** (Scheme 2-6). Similar to the results with **19**, there was a consistency between the ratio of preformed (*Z*)-enol borinate **21** to lithium enolate and the *syn:anti* ratio of aldol adducts **25** obtained after aldolization with PhCHO following borylation. These observations further supported the conclusion that isomerization of (*Z*)-enol borinates under conditions required for borylation of lithium enolates is unlikely. Hence, the formation of (*E*)-enol borinates arising from borylation of lithium (*Z*)-enolates should occur via a pathway other than *O*-borylation.

Scheme 2-6.[a] Borylation of lithium (*Z*)- and (*E*)-enolates of **24** in presence of (*Z*)-enol borinate **21**.



[a] Reaction conditions: (a) Preformed Li and B enolate solutions in toluene-d_8 was mixed at –42 °C followed by addition of (*c*-Hex)$_2$BCl (5.0 equiv, 1.0 M in tolutene-d_8). Ratio of (*E*)- and (*Z*)-enol borinate was determined by direct ^{1}H NMR at –42 °C. (b) Li (*E*)-enolate formation by addition of **24** (0.80 M in THF) to LiN(TMS)*t*-Bu (0.20 M in THF). Addition of preformed (*Z*)-enol borinate **21** (0.5 M in C_6H_6) at –78 °C followed by (c-Hex)$_2$BCl (1.6 equiv, 1.0 M in hexane) then stirring at –42 °C, and aldolization with PhCHO (5.0 equiv) at –78 °C. The yield (by ^{1}H NMR) of the aldol products was within the range of 95-99% by comparison of crude aldol with trichloroethylene as the internal standard. See Experimental Section for detailed procedure.

In summary, the obtained results have shown that (*Z*)-enol borinates are thermodynamically favored and cannot be isomerized to the (*E*)-isomer under lithiation/borylation conditions. Thus, *O*-borylation followed by isomerization of the (*Z*)-enol borinate, as previously reported by Kundu,[31] is not a plausible explanation for the highly selective formation of (*E*)-enol borinates. Alternatively, *C*-borylation of the lithium enolates would generate an unstable α-boryl ketone that would be expected to readily rearrange to the enol borinate. If this rearrangement were highly stereoselective, the observed results could be easily explained. Although no experimental study has been pursued toward this hypothesis, a computational study of the stereoselectivity of α-boryl ketones to enol borinates is underway.[34]

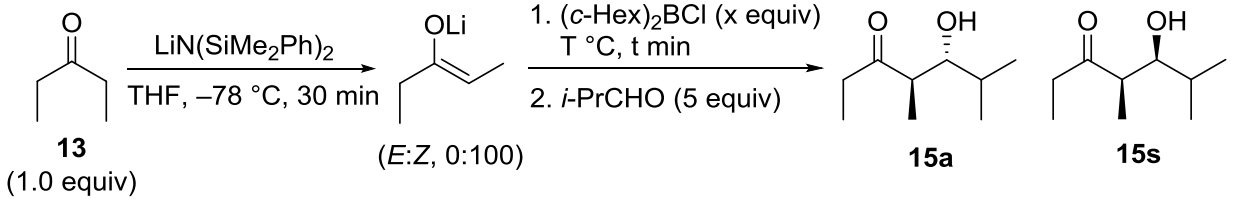
2.3 Application of the method

2.3.1 Unusual borylation kinetics

It is interesting that the borylation of the Li (*Z*)-enolate of 3-pentanone **13** was a facile process, with 90% conversion to the (*E*)-enol borinates within 5 min at –78 °C (Table 2-6, entry 1). However, full conversion toward (*E*)-enol borinates was difficult to achieve at this temperature, and the conversion increased only by 3% when increasing reaction time by a factor of 10 (Table

2-6, entry 2). Doubling the amount of (*c*-Hex)$_2$BCl (entry 3) or increasing temperature and reaction time (entry 4) helped to drive the borylation to completion. These observations led to a hypothesis that there is formation of a persistent borate-type complex between the newly-formed enol borinates and the unreacted lithium enolates, reducing the reactivity of the lithium enolates, and thus inhibiting full borylation.

Table 2-6. Dependence of borylation of lithium (*Z*)-enolate of 3-pentanone on reaction time, temperature and amount of (*c*-Hex)$_2$BCl.[a]

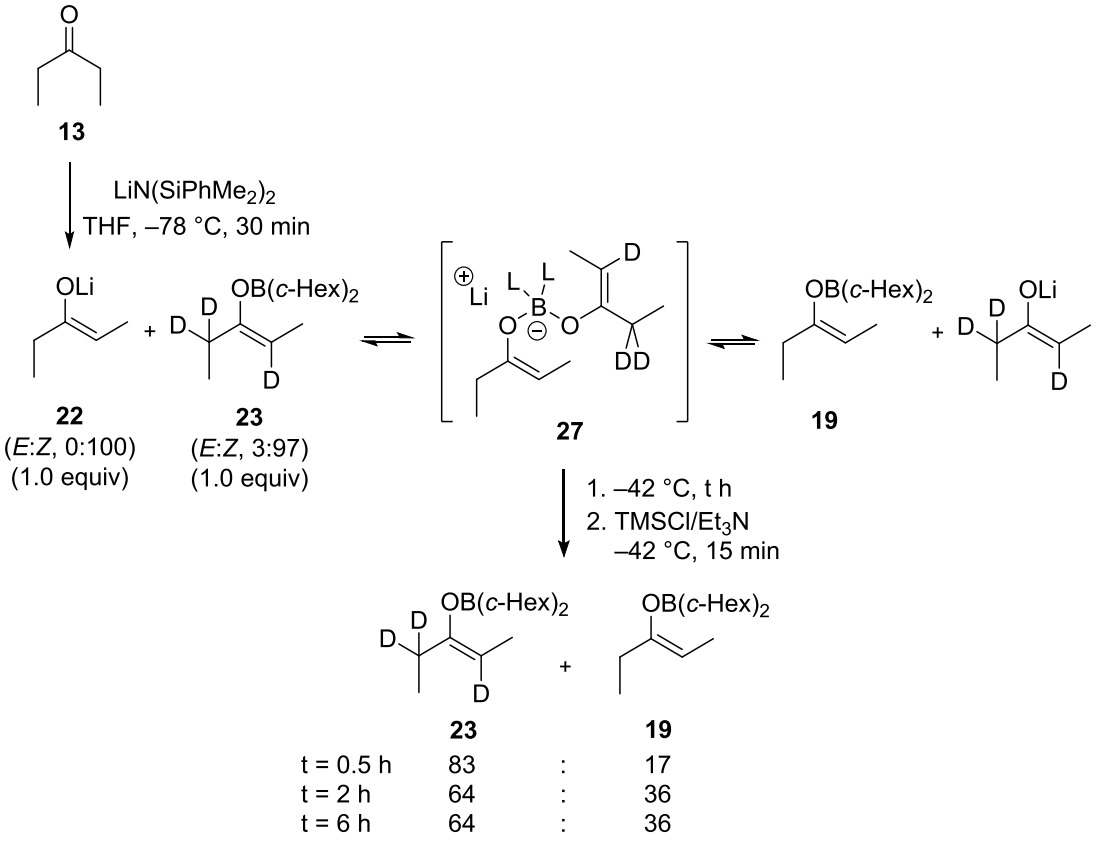


entry	x	T	t	**15a**:**15s**[b]
1	1.6 equiv	–78 °C	5 min	90:10
2	1.6 equiv	–78 °C	60 min	93:7
3	3.2 equiv	–78 °C	60 min	98:2
4	1.6 equiv	–42 °C	120 min	98:2

[a] Reaction conditions: Enolate formation by addition of **13** (0.95 M in THF) to LiN(SiMe$_2$Ph)$_2$ (0.20 M in THF) at –78 °C. Borylation by addition of (*c*-Hex)$_2$BCl (1.6 equiv, 1.0 M in hexane) and aldolization by addition of *i*-PrCHO (5.0 equiv) at –78 °C. In all cases, the yield of the aldol products was within the range of 92–97% by comparison of crude aldol products with trichloroethylene as the internal standard. See Experimental Section for detailed procedure.
[b] Determined by analysis of ^{1}H NMR spectra of the crude reaction mixtures.

Deuterium labelling experiments were designed to find direct evidence of borate complex formation. Deuterated (*Z*)-enol borinate **23** and protonated lithium (*Z*)-enolate **22** were chosen as the starting enolates. After mixing the two enolates for a variable amount of time, the lithium enolates were quenched by addition of Me$_3$SiCl. The remaining enol borinates were a mixture of deuterated and protonated forms (Scheme 2-7). The most plausible explanation for this observation is via association/dissociation process of a 'borate' complex. With an initial 1:1 ratio of **23**:**22**, the expected ratio for **23**:**19** at equilibrium would be close to 1:1, since the energy of the two enolate isotopologues is expected to be approximately equal. However, the observed ratio of **23**:**19** was 1.8:1 after 2 h and remained unchanged after an additional 4 h, suggesting equilibrium had been reached. This unexpected observation might have resulted from adventitious moisture that could quench Li enolate **22**, making the actual ratio of **23**:**22** greater than 1:1.

Scheme 2-7.[a] Deuterium exchange between protonated Li enolate **22** and deuterated enol borinate **23**.

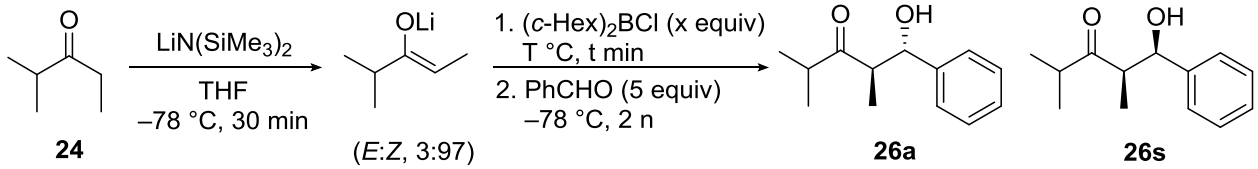


[a] Reaction conditions: Formation of **22** by addition of **13** (0.95 M in THF) to $LiN(SiMe_2Ph)_2$ (0.20 M in THF) at –78 °C. Addition of **23** (1.6 equiv, 1.0 M in hexane) to **22** at –42 °C and stirring at –42 °C then removal of Li enolates by addition of Me_3SiCl/Et_3N. The ratio of **19** and **23** was determined by ^1H NMR of the crude mixture after removal of the volatiles under vacuum. See Experimental Section for detailed procedure.

Similar to the lithium (*Z*)-enolate of **13**, the borylation of the lithium (*Z*)-enolate of **24** at –78 °C was initially fast, 65% conversion to the (*E*)-enol borinate after 5 min, but the conversion was unchanged after an hour at this temperature (Table 2-7, entries 1, 2). It is noticeable that the conversion of borylation of lithium enolate of **24** was significantly lower than that of **13**, and that increasing the borylation temperature and time only resulted in a very small increase of the conversion (Table 2-7, entry 3). This observation could not be clearly explained with the hypothesis proposing the formation of **27**, because the previous results from borylation of lithium

enolate of **13** suggested only small amounts (ca. 7-10%) of complex **27** can be present at –78 °C (cf. Table 2-6, entry 2).

Table 2-7. Dependence of borylation of Li (*Z*)-enolate of 2-methyl-3-pentanone on reaction time and amount of (*c*-Hex)$_2$BCl.[a]



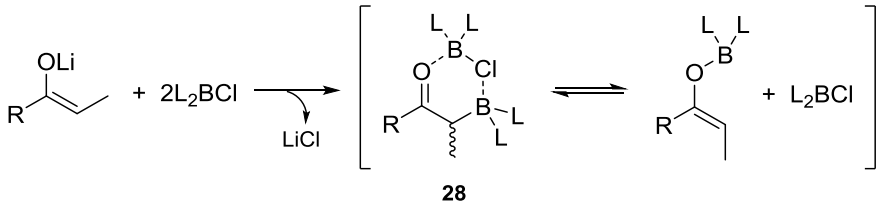
24 (*E*:*Z*, 3:97) **26a** **26s**

entry	x	T	t	**26a**:**26s**[b]
1	1.6 equiv	–78 °C	5 min	65:35
2	1.6 equiv	–78 °C	60 min	65:35
3	1.6 equiv	–42 °C	120 min	70:30
4	2.0 equiv	–42 °C	120 min	76:24
5	4.0 equiv	–42 °C	120 min	94:6

[a] Reaction conditions: Enolate formation by addition of **24** (0.80 M in THF) to LiN(SiMe$_3$)$_2$ (0.20 M in THF) at –78 °C. Borylation by addition of (*c*-Hex)$_2$BCl (1.6 equiv, 1.0 M in hexane), followed by aldolilzation with PhCHO (5.0 equiv) at –78 °C. In all cases, the yield (by ^{1}H NMR) of the aldol products was within the range of 95-99% by comparison of crude aldol with trichloroethylene as the internal standard. See Experimental Section for detailed procedure. [b] Determined by ^{1}H NMR of the crude reaction mixture.

Results from the borylation study of **24** suggest that there might be processes other than formation of (*E*)-enol borinate from reaction of lithium enolate with dialkylboron chloride. Arising from the observations that the maximum conversion of borylation of the lithium enolate of **24** was ca. 70% with 1.6 equiv of dialkylboron chloride (Table 2-7, entry 3), the borylation of Li enolate with (*c*-Hex)$_2$BCl is hypothesized to occur in a ca. 1:2 stoichiometric ratio. This unusual stoichiometric ratio might result from a plausible bridged complex **28** formed from the α-boryl ketone and the dialkylboron chloride (Scheme 2-8). As a result, higher borylation conversion might be achieved by increasing the amount of dialkylboron chloride. Consistent with this hypothesis, the ratio of *anti*-product **26a** increased with increasing amounts of dialkylboron chloride used (Table 2-7, entries 3-5).

Scheme 2-8. Proposed hypothesis for 2:1 stoichiometric ratio in borylation of lithium enolate.

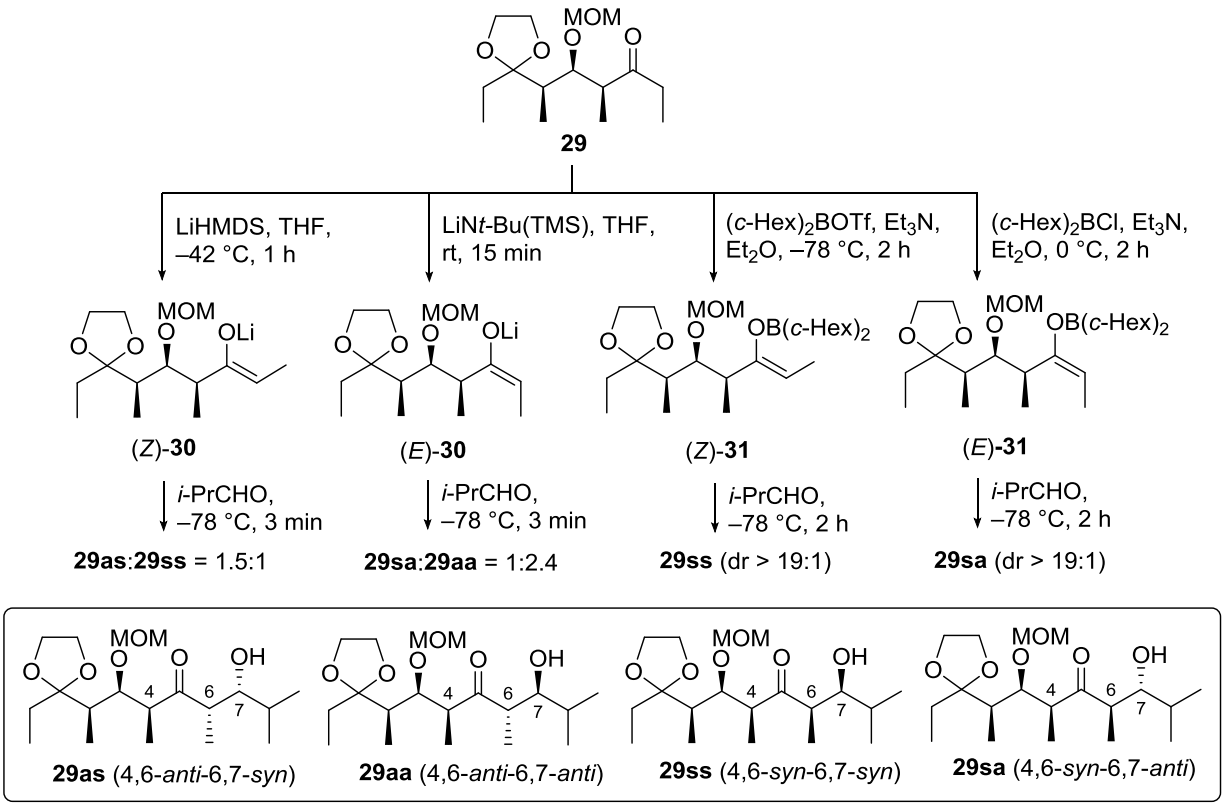


28

2.3.2 Dependence of the conversion on reaction conditions

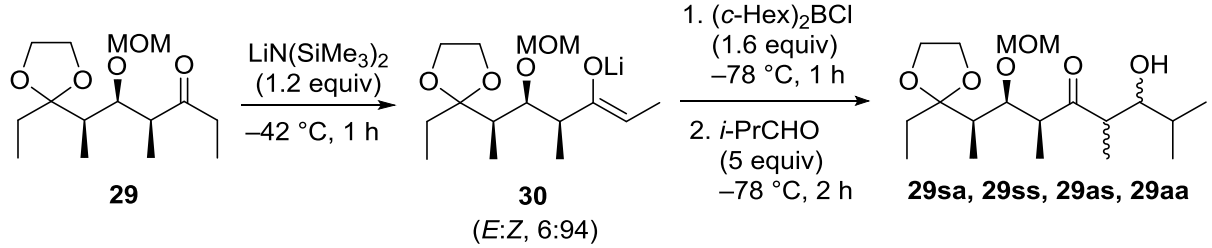
Because the rate of borylation of Li enolates of simple ketones is fast and both lithium enolates and enol borinates produce the same aldol adducts, it is difficult to study the influence of reaction conditions on the borylation process. Hence, ketone **29,** whose Li and B (*Z*)- and (*E*)-enolates give distinct diastereoselectivities in their aldol reactions with *i*-PrCHO (Scheme 2-9),[35] was chosen as a model ketone to probe the dependence of borylation on reaction conditions (temperature, time, amount of dialkylboron chloride and concentration).

Scheme 2-9. Distinct diastereoselectivities in aldol reaction of different metal enolates of **29** and *i*-PrCHO.



As previously proposed from the study on borylation of lithium enolates of **13** and **24**, the inhibition of full borylation might result from the formation of the boron complexes similar to **27** and **28** that can reduce the reactivities of the lithium enolate and dialkylboron chloride (Schemes 2-7 and 2-8). Consequently, decreasing the reaction concentration could potentially drive the equilibrium toward the dissociation of these complexes, thus accelerating the borylation process. Therefore, the influence of concentration on borylation of the $LiN(SiMe_3)_2$-generated lithium (*Z*)-enolate **30**, prepared from ketone **29**, was studied. Solutions of **30** (*E*:*Z*, 6:94) at –78 °C with three different concentrations were subjected to borylation using $(c\text{-Hex})_2BCl$ (Table 2-8).

Table 2-8. Dependence of borylation of Li (*Z*)-enolate **30** on concentration.[a]



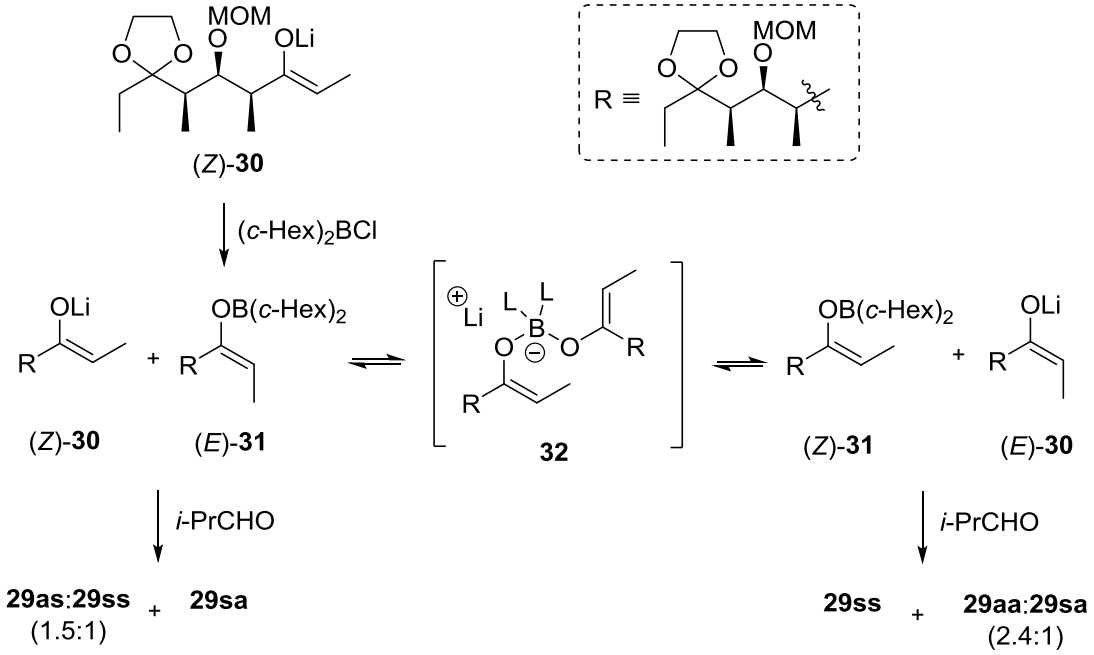
entry	nominal concentration of **30**		aldol products
	before adding $(c\text{-Hex})_2BCl$	after adding $(c\text{-Hex})_2BCl$	**29sa**:**29ss**:**29as**:**29aa**[b]
1	0.14 M	0.1 M	57:20:15:8
2	0.08 M	0.07 M	64:16:14:6
3	0.05 M	0.04 M	77:10:9:4

[a] Reaction conditions: Formation of (*Z*)-**30** by addition of **29** (0.20 M in THF) to $LiN(SiMe_3)_2$ at –42 °C. Borylation by addition of $(c\text{-Hex})_2BCl$ (1.6 equiv, 1.0 M in hexane) to solutions of **30** in THF at –78 °C and aldolization with *i*-PrCHO (5.0 equiv) at –78 °C. In all cases, the conversion (by ^1H NMR) of the aldol products was within the range of 92–97%. See Experimental Section for detailed procedure. [b] Determined by ^1H NMR of the crude reaction mixture.

It is interesting that the amounts of **29ss** and **29aa** in the product mixtures shown in Table 2-8 were higher than expected. If the mixture of enolates present before aldol reaction included only the products of borylation (i.e., (*E*)-**31**, and unreacted lithium enolates (*Z*)-**30** and (*E*)-**30**), the ratio of the two *syn*-aldol products should favour **29as** over **29ss**. This ratio is expected because the product ratio from the aldol reaction of (*Z*)-**30** is known[35] to give **29as** predominantly. Similarly, **29aa** is the major product from the aldol reaction of lithium enolate (*E*)-**30** and exclusively arises from this pathway.[35] Consequently, the amount of **29aa** should not exceed 6%, the initial amount of (*E*)-**30** before borylation. The inconsistency between the expected and obtained results suggests

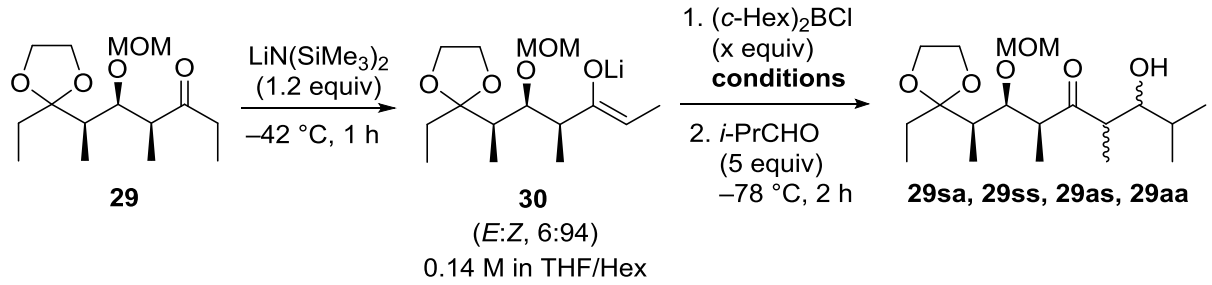
that additional amounts of (*E*)-**30** and (*Z*)-**31** might be generated via the association/dissociation of 'borate' complex **32** (Scheme 2-10).

Scheme 2-10. Mechanistic rationale for the unexpected distributions of **29ss** and **29aa** in the products obtained after borylation of (*Z*)-**30** followed by aldol reaction with *i*-PrCHO.



The obtained results in Table 2-8 show a trend of increasing both borylation conversion and selectivity toward the (*E*)-enol borinates with decreasing concentration. This suggests that the formation of the borate complexes can be mitigated by executing the reaction in diluted media. However, performing the reaction at lower concentration is not beneficial in many ways, especially when the transformation needs to be done on scale. Therefore, the optimization of borylation condition on lithium (*Z*)-enolate **30** was continued studying at ca. 0.1 M (Table 2-9).

Table 2-9. Dependence of borylation conversion of **30** on stoichiometry of dialkylboron chloride, reaction time and temperature.[a]



entry	conditions	aldol products **29sa**:**29ss**:**29as**:**29aa**[b]
1	x = 1.6 equiv, –78 °C, 5 min	48:20:13:19
2	x = 0.6 equiv, –78 °C, 1 h	37:28:25:10
3	x = 1.0 equiv, –78 °C, 1 h	53:20:16:11
4	x = 1.6 equiv, –78 °C, 1 h	63:17:11:9
5	x = 1.6 equiv, –78 °C, 2 h	66:17:11:6
6	x = 1.6 equiv, –78 °C, 4 h	66:17:11:6
7	x = 1.6 equiv, –78 °C, 1 h then –42 °C, 1 h	86:7:4:3
8	x = 1.6 equiv, –42 °C, 1 h	88:6:3:3
9	x = 2.2 equiv, –42 °C, 1 h	97:3

[a] Reaction conditions: Formation of (*Z*)-**30** by addition of **29** (0.20 M in THF) to $LiN(SiMe_3)_2$ (0.60 M in THF) at –42 °C. Borylation by addition of $(c\text{-Hex})_2BCl$ (1.6 – 2.2 equiv, 1.0 M in hexane) at –78 °C and stirring at indicated temperature, and after indicated time, followed by addition of *i*-PrCHO (5.0 equiv) –78 °C then quenching and workup after stirring at –78 °C for 2 h. In all cases, the conversion (by ^{1}H NMR) of the aldol products was within the range of 92–97%. See Experimental Section for detailed procedure. [b] Determined by ^{1}H NMR of the crude reaction mixture.

As expected from the unusual borylation kinetics previously discussed, borylation of lithium (*Z*)-enolate **30** using 1.6 equiv. of $(c\text{-Hex})_2BCl$ at –78 °C already resulted in ca. 50% conversion to the (*E*)-enol borinate within 5 min (Table 2-9, entry 1). Extending borylation time (1-4 h, entries 4-6) gave a slight increase in conversion to a maximum of ca. 70% after 1 h and remained unchanged after 4 h, suggesting that the borylation was initially fast then either proceeded very slowly at –78 °C (perhaps due to the unusual [$2L_2BCl$•Li enolate] and [enol borinate•Li enolate] complexes) or stopped (inefficient amount of boron reagent). However, the latter possibility is unlikely because the borylation continued when the temperature was increased from –78 to –42 °C (entry 7). Moreover, the results from borylations using increasing amounts of dialkylboron

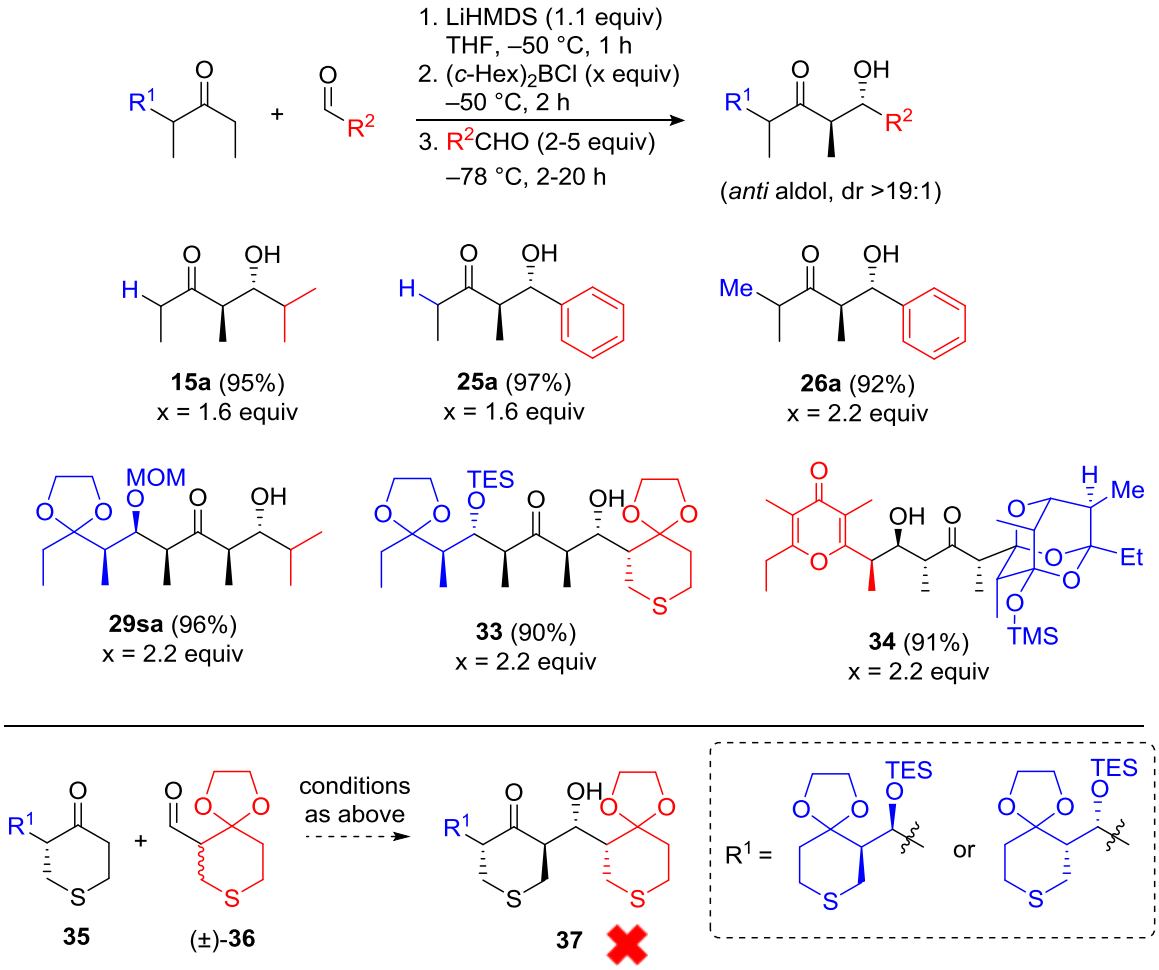
chloride (Table 2-9, entries 2-4) showed a nearly linear trend in increasing the conversion toward **29sa**. Hence, the formation of (*E*)-**31** at low temperature apparently required two equivalents of dialkylboron chloride. This observation further supports the hypothesis of formation of boron complex **28** (cf. Scheme 2-8). Increasing the reaction temperature presumably promotes dissociation of the complex, releasing free dialkylboron chloride and continuing the borylation. Therefore, the inhibition of full borylation can be overcome by performing borylation at higher temperature (entries 7, 8). Finally, full borylation can be achieved within 1 h at –42 °C by increasing the amount of dialkylboron chloride to 2.2 equivalents (entry 9).

In summary, as described for both simple and complex ketones, full borylation of lithium enolates is inhibited at –78 °C, most likely due to the formation of **28** or related complexes. This inhibition can be overcome by altering the reaction conditions toward disfavoring the formation of the complex; e.g., increasing reaction time, temperature, and(or) amount of dialkylboron chloride, and decreasing the reaction concentration.

2.3.3 Substrate scope and relative reactivity of enol borinate diastereomers

With a better understanding of the dependence of the borylation on the reaction conditions as described in sections 2.2.1 and 2.2.2 above, a series of ethyl ketones with increasing structural complexity were subjected to the optimized lithiation – borylation conditions followed by addition of aldehyde. In each case, the *anti*-aldol adduct was obtained with high stereoselectivity and yields, that are comparable or superior to the previously reported analogous reactions via 'soft' enolization. The aldol reactions of the (*E*)-enol borinates generated from this process were not limited to *i*-PrCHO (Scheme 2-11, compounds **25a**, **26a**, **33**,[36] and **34**[31]). This method also exhibited good protecting group tolerance (Scheme 2-11, compound **29sa** and **33**). It is particularly noteworthy in case of compound **34**, key precursor to *ent*-caloundrin B. As previously reported,[23] attempts to generate the required (*E*)-enol borinate of the parent ketone **2** via 'soft' enolization gave very low conversion toward the desired aldol adduct **34**. Reported borylation of the Li (*E*)-enolate was successful but produced only a moderate yield of the desired aldol adduct **34**. In contrast, applying the optimized borylation conditions to prepare the required (*E*)-enol borinate gave **34** in excellent yield and with high stereoselectivity.[31]

Scheme 2-11. Substrate scope for lithiation-borylation-aldolization route to *anti* aldol product.

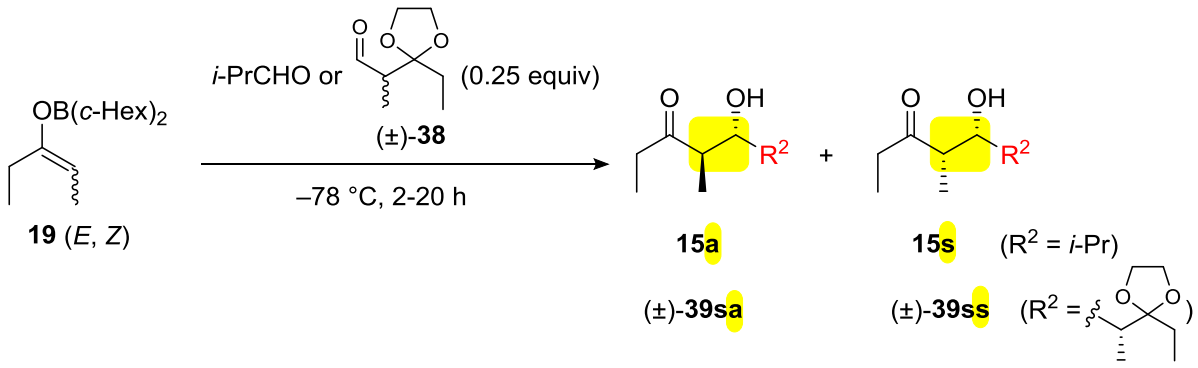


In contrast to D. Kundu's report[31] (cf. Scheme 1-12), the method failed to produce enol borinates from lithium (*Z*)-enolates of cyclic ketones **35** (Scheme 2-11). The desired products **37** were not successfully obtained and the starting ketones **35** were not recovered after the reaction. It is suspected that borylation of the lithium enolates of **35** might have resulted in ring opening of thiopyran instead of formation of enol borinates.

The relative reactivity of (*E*)- and (*Z*)-enol dicyclohexylborinate towards representative aldehydes was also measured using 3-pentanone as the model ketone. Treatment of the enol borinate **19** (*E*:*Z* = 73:27) with a deficient amount of *i*-PrCHO (0.25 equiv) gave a 50:1 mixture of **15a**:**15s**, respectively (Table 2-10, entry 1), implying that (*E*)-**19** is ca. 18 times more reactive than (*Z*)-**19**. This result stands in stark contrast to D. Kundu's report for the same reaction[30] (relative reactivity *E*:*Z* = 2:1; cf. Table 1-4, entries 1, 2). Treatment of the enol borinate **19** (*E*:*Z* = 63:37)

with a deficient amount of (±)-**38** (0.25 equiv) gave a 30:1 mixture of (±)-**39sa**:(±)-**39ss**, respectively (Table 2-10, entry 2), suggesting the reactivity of (*E*)-**19** towards the chiral aldehyde is also ca. 18 times more than that of (*Z*)-**19**. To the best of my knowledge, this is the first report on relative reactivity of enol borinate diastereoisomers, which potentially provides a useful synthetic tool to enhance the diastereoselectivity toward *anti* aldol product via kinetic resolution.

Table 2-10. Relative reactivity of enol borinate **19** diastereomers.



entry	(*E*)-**19**:(*Z*)-**19**[a]	R^2CHO	products[b]
1	73:27	*i*-PrCHO	**15a**:**15s** (50:1)
2	63:37	(±)-**38**	(±)-**39sa**:(±)-**39ss** (30:1)

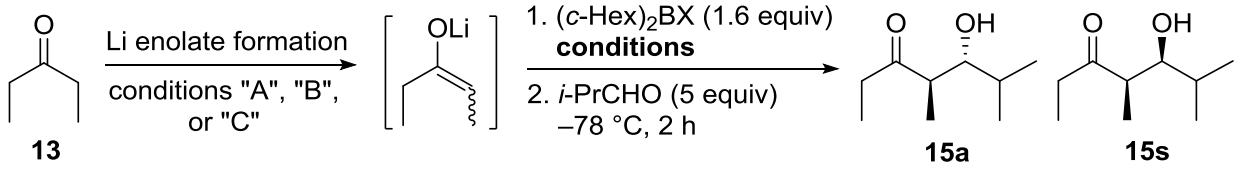
[a] The indicated diastereomer ratios of the enol borinates were determined by ^{1}H NMR. [b] Determined by ^{1}H NMR of the crude reaction mixture after work up.

2.4 Study on borylation using other boron reagents

The use of other boron reagents was examined to determine the scope of the method. Borylation of $LiN(SiMe_3)_2$-generated Li enolate of **13** (*E*:*Z*, 34:66) with $(c\text{-Hex})_2BOTf$ at –42 °C for 2 h followed by aldolization with *i*-PrCHO gave a 52:48 mixture of **15a** and **15s**, respectively (Table 2-11, entry 3). This result was inconsistent with Kundu's report[30] (**15a**:**15s**, 8:1; cf. Table 1-5, entry 2). Direct ^{1}H NMR measurement of the enolate mixture at –42 °C prior to aldolization showed only enol dicyclohexylborinates with an *E*:*Z* ratio of 51:49, consistent with the subsequent aldol product ratio. Similar aldol diastereoselectivites were obtained when borylating $LiN(i\text{-Pr})_2$- and $LiN(SiMe_2Ph)_2$-generated Li enolates of **13** (*E*:*Z*, 70:30 and 0:100, respectively), followed by aldolization with *i*-PrCHO (Table 2-11, entries 4, 5). The different product ratios obtained when using $(c\text{-Hex})_2BOTf$ versus $(c\text{-Hex})_2BCl$ under otherwise identical conditions (Table 2-11, entries 1, 3, and 2, 5) suggested that the leaving group had a significant influence on the borylation

stereoselectivity. This result is in stark contrast with Kundu's conclusion that the leaving group had a minimal effect on the diastereoselectivity[30] (cf. Table 1-5, entries 1, 2).

Table 2-11. Borylation on Li enolate of **13** using (*c*-Hex)$_2$BX.



13 **15a** **15s**

"A": LiN(SiMe$_3$)$_2$ (1.2 equiv)
THF, –78 °C, 30 min (*E*:*Z*, 34:66)
"B": LiN(*i*-Pr)$_2$ (1.2 equiv)
THF, –78 °C, 30 min (*E*:*Z*, 70:30)
"C": LiN(SiMe$_2$Ph)$_2$ (1.2 equiv)
THF, –78 °C, 30 min (*E*:*Z*, 0:100)

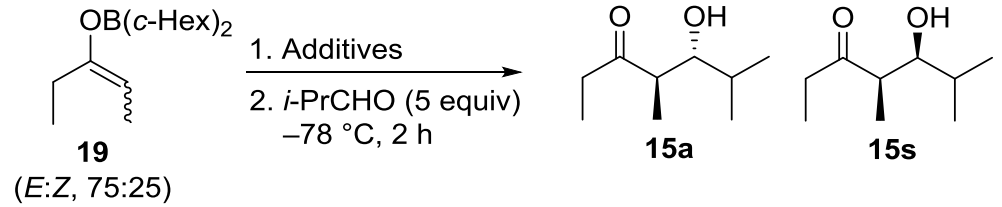
entry	Li enolate conditions[a]	borylation conditions	boron enolate *E*:*Z*[b]	**15a**:**15s**[c]
1	A	L$_2$B-X = (*c*-Hex)$_2$BCl; –42 °C, 2 h	95:5	95:5
2	B	L$_2$B-X = (*c*-Hex)$_2$BCl; –42 °C, 2 h	-	95:5
3	A	L$_2$B-X = (*c*-Hex)$_2$BOTf; –42 °C, 2 h	51:49	51:49
4	A	L$_2$B-X = (*c*-Hex)$_2$BOTf; –42 °C, 2 h	-	49:51[d]
5	B	L$_2$B-X = (*c*-Hex)$_2$BOTf; –42 °C, 2 h	-	55:45
6	C	L$_2$B-X = (*c*-Hex)$_2$BOTf; –42 °C, 2 h	-	51:49

[a] Reaction conditions: Enolate formation by addition of **13** (0.95 M in THF) to amide base (0.20 M in THF) at –78 °C. Borylation by addition of L$_2$BX (1.6 equiv), followed by aldolilzation with *i*-PrCHO (5.0 equiv) at –78 °C. The yield (by ^{1}H NMR) of the aldol products in all cases was within the range of 90-95% by comparison of crude aldol with trichloroethylene as the internal standard. See Experimental Section for detailed procedure. [b] Determined by analysis of ^{1}H NMR spectrum at –42 °C in toluene-d$_8$ of the crude enolate mixture before aldolization. [c] Determined by analysis of ^{1}H NMR spectrum of the crude aldol products after workup. [d] Slow addition of (c-Hex)$_2$BOTf in 1 h at –42 °C.

It was initially hypothesised that the lower stereoselectivity observed in borylation using (*c*-Hex)$_2$BOTf compared with (*c*-Hex)$_2$BCl might be the result of triflate-mediated isomerization toward the more thermodynamically favoured (*Z*)-enol borinate. This hypothesis was tested by adding the related reagents to preformed enol borinate **19** (Table 2-11). Using (*c*-Hex)$_2$BOTf as an additive did not cause any change in the diastereomer ratio of **19** (entries 5, 6), implying that the excess 0.6 equiv. of (*c*-Hex)$_2$BOTf present in the borylation of the lithium enolate of **13** did not induce the isomerization of the enol borinates. The by-product of the borylation reaction, LiOTf, was also added to enol borinate **19** and showed no effect on the boron enolate geometry. It was

also hypothesised that the borylation using a boron triflate might be more exothermic than that of a dialkylboron chloride, and this might increase the temperature of the reaction mixture and thereby accelerate the isomerization rate. However, slow addition of the boron triflate also gave a ca. 1:1 mixture of **15a** and **15s** (Table 2-11, entry 4). These observations suggest that the leaving group has a significant effect on the stereoselectivity of the borylation; however, the origin of this difference is not due to triflate-mediated isomerization of enol borinates.

Table 2-12. Screening of additives related to the triflates-involved borylation conditions.[a]



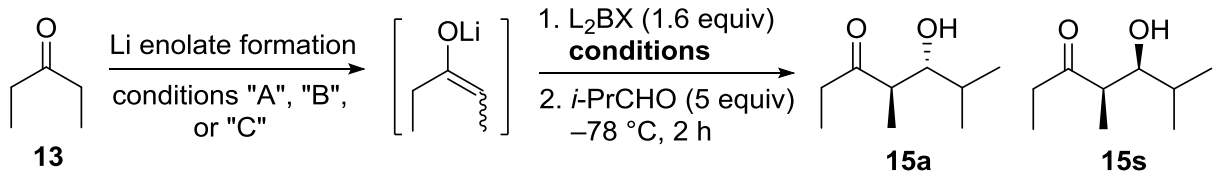
19 (*E*:*Z*, 75:25) **15a** **15s**

entry	additives	conditions	**15a**:**15s**[b]
1	None	–42 °C, 2 h	77:23
2	(*c*-Hex)$_2$BOTf	–42 °C, 2 h	79:21
3	(*c*-Hex)$_2$BOTf + HMDS	–42 °C, 2 h	80:20
4	LiOTf	–42 °C, 2 h	72:28

[a] Reaction condition: Addition of additives (1.0 equiv, 'neat' in cases of the amines, or as solution in THF/hexane) to **19** (0.20 M in THF) at –42 °C, and after indicated time, addition of *i*-PrCHO (5.0 equiv) at –78 °C followed by quench and workup after stirring for 2 h. See Experimental Section for detailed procedure. [b] Determined by ^{1}H NMR of the crude reaction mixture.

An analogous set of borylation reactions of the Li enolate of **13** using Bu_2BOTf was executed. Direct ^{1}H NMR measurement of the enolate mixture at –42 °C after borylation of the LiN(SiMe$_3$)$_2$-generated Li enolate of **13** for 2 h –42 °C showed only enol dibutylborinates with an *E*:*Z* ratio of 52:48; subsequent aldolization with *i*-PrCHO gave the corresponding aldol products **15a** and **15s** with the expected ratio (Table 2-12, entry 1). Extension of thr borylation time to 4 h did not change the diastereoselectivity of the aldol reaction, which suggested that isomerization was not occurring (entry 2). Consistently, borylation of LiN(*i*-Pr)$_2$- and LiN(SiMe$_2$Ph)$_2$-generated Li enolates of **13** (*E*:*Z*, 70:30 and 0:100, respectively) with Bu_2BOTf followed by aldolization afforded the aldol products **15a** and **15s** in ratio of ca. 1:1 (entries 3, 4). The diastereoselectivity of borylation using Bu_2BOTf was similar to that of (*c*-Hex)$_2$BOTf, suggesting that the bulkiness of the boron ligand had little effect on the stereoselectivity of enol borinate formation.

Table 2-13. Boron reagent scope of borylation on Li enolate of **13**.



13 **15a** **15s**

"A": $LiN(SiMe_3)_2$ (1.2 equiv)
THF, –78 °C, 30 min (*E*:*Z*, 34:66)
"B": $LiN(i\text{-}Pr)_2$ (1.2 equiv)
THF, –78 °C, 30 min (*E*:*Z*, 70:30)
"C": $LiN(SiMe_2Ph)_2$ (1.2 equiv)
THF, –78 °C, 30 min (*E*:*Z*, 0:100)

entry	Li enolate conditions[a]	borylation conditions	enol borinate *E*:*Z*[b]	**15a**:**15s**[c]
1	A	L_2B-X = Bu_2BOTf; –42 °C, 2 h	52:48	51:49
2	A	L_2B-X = Bu_2BOTf; –42 °C, 4 h	-	52:48
3	B	L_2B-X = Bu_2BOTf; –42 °C, 2 h	-	54:46
4	C	L_2B-X = Bu_2BOTf; –42 °C, 2 h	-	47:53
5	A	L_2B-X = 9-BBNOTf; –42 °C, 2 h	-	37:63
6	B	L_2B-X = 9-BBNOTf; –42 °C, 2 h	-	35:65
7	A	L_2B-X = 9-BBN-Cl; –42 °C, 2 h	-	30:70

[a] Reaction condition: Enolate formation by addition of **13** (0.95 M in THF) to amide base (0.20 M in THF) at –78 °C. Borylation by addition of L_2BX (1.6 equiv), followed by aldolilzation with *i*-PrCHO (5.0 equiv) at –78 °C. Except for 9-BBN-X, the yield (by ^1H NMR) of the aldol products in all cases was within the range of 90-95% by comparison of crude aldol with trichloroethylene as the internal standard. See Experimental Section for detailed procedure. [b] Determined by analysis of ^1H NMR spectrum at –42 °C in toluene-d_8 of the crude enolate mixture before aldolization. [c] Determined by analysis of ^1H NMR spectrum of the crude aldol products after workup.

Finally, borylations of the lithium enolate of **13** using 9-BBN-OTf and 9-BBN-Cl were compared to expand the study on the reagent scope. Borylation of the $LiN(SiMe_3)_2$-generated Li enolate of **13** for 2 h –42 °C followed by aldolization gave similar mixtures of **15a** and **15s** (ca. 1:2, respectively) (Table 2-11, entries 10 – 12). Surprisingly, the yields of aldol products from these reactions were much lower (ca. 40-50%) than those using $(c\text{-Hex})_2BCl$, $(c\text{-Hex})_2BOTf$, and Bu_2BOTf (ca. 91-97%), thereby preventing a direct comparison.

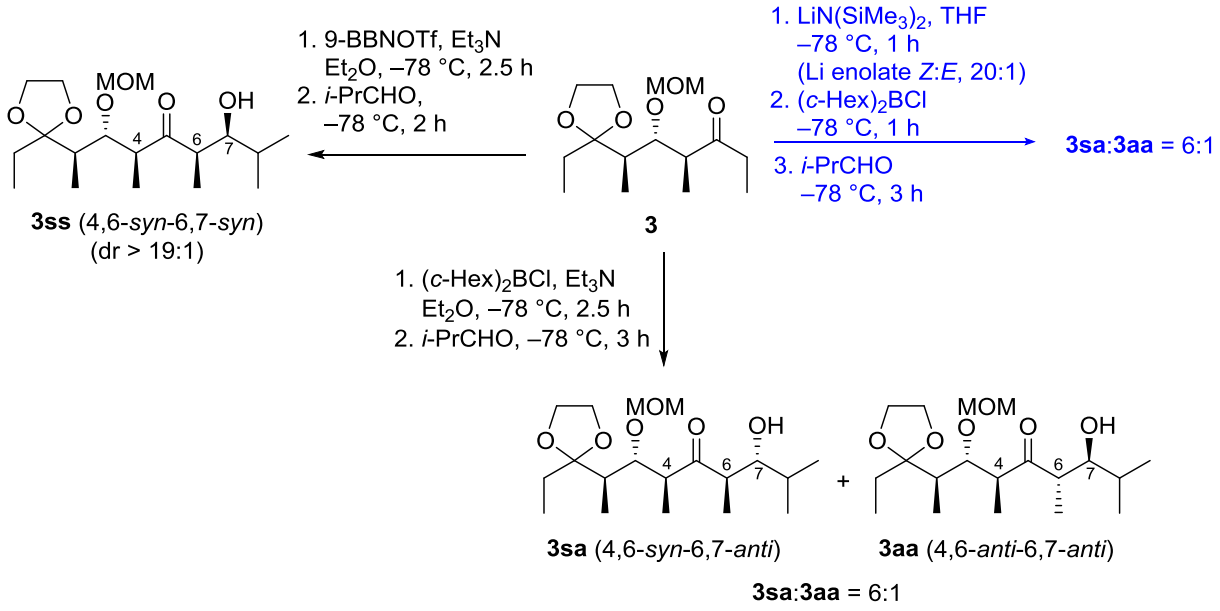
In summary, the study on lithiation/borylation of ethyl ketones with selected boron reagents revealed that highly stereoselective formation of (*E*)-enol borinates is limited to $(c\text{-Hex})_2BCl$. The

analogous use of (c-Hex)$_2$BOTf was not stereoselective and similar results were obtained with Bu_2BOTf, 9-BBN-Cl, and 9-BBN-OTf.

3 CONCLUSION

Treatment of the Li (*Z*)-enolate of **3** with (*c*-Hex)$_2$BCl followed by addition of excess *i*-PrCHO produced the *anti*-adducts **3sa** and **3aa** selectively (Scheme 3-1).[24] This serendipitous observation implied that the aldol reaction had occurred via an (*E*)-enol borinate, and inspired a detailed study of the borylation of lithium enolates within the Ward Group. The objective of this M.Sc. project was to investigate the origin of this highly selective formation of (*E*)-enol borinates as well as scope and limitations of the method.

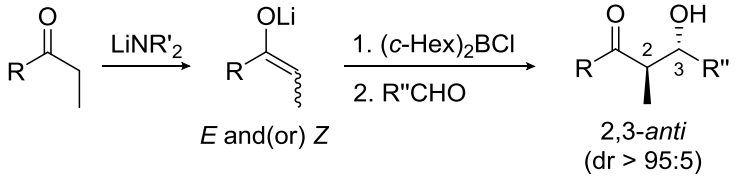
Scheme 3-1. Serendipitous observation of highly selective formation of the (*E*)-enol borinate via borylation of lithium (*Z*)-enolate of **3**.



The results of this project show that ketone-derived lithium enolates undergo facile borylation with (*c*-Hex)$_2$BCl and after addition of an aldehyde to generate the *anti* aldol adduct with high diastereoselectivity, regardless of the method of producing the Li enolate or its starting geometry. This lithiation/borylation method has been implemented successfully across a range of ethyl ketones with increasing structural complexity with results that are comparable or superior to previously reported analogous reactions via 'soft' enolization. The selectivity toward the *anti* aldol product can potentially be further enhanced via kinetic resolution, because the reactivity of the (*E*)-enol borinate is considerably greater than the (*Z*)-isomer. However, the high stereoselectivity toward the *anti* product from this method was obtained only with the use of (*c*-Hex)$_2$BCl in the

borylation step. Analogous use of (*c*-Hex)$_2$BOTf, Bu$_2$BOTf, 9-BBNCl, or 9-BBNOTf resulted in the loss of diastereoselectivity.

Scheme 3-2. Summary of lithiation/borylation method for ethyl ketones.

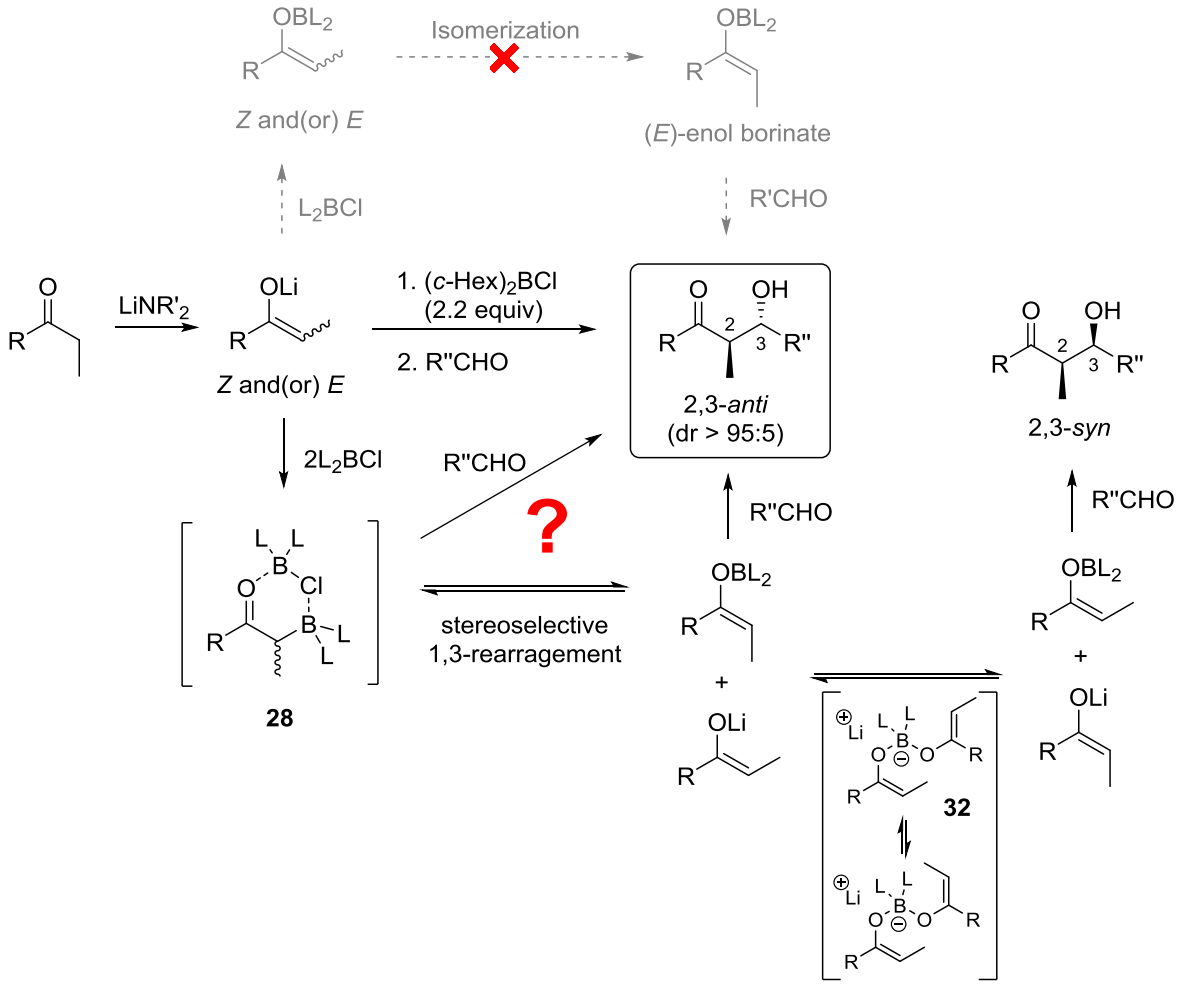


Both computational and experimental data supported that ketone-derived (*Z*)-enol dialkylborinates are the thermodynamically favoured isomer. A study on the potential for the (*Z*)-enol borinate to isomerize showed that conversion to the (*E*)-isomer was negligible under conditions similar to those for borylation of the corresponding lithium enolate. Thus, *O*-borylation of the lithium (*Z*)-enolate followed by isomerization of the resulting (*Z*)-enol borinate, as previously reported by Kundu,[31] is not a plausible explanation for the highly selective formation of the (*E*)-enol borinate. Alternatively, the formation of α-boryl ketone via *C*-borylation of the lithium enolate followed by stereoselective 1,3-boratropic rearrangement to enol borinate is proposed and being investigated computationally (Scheme 3-3).[34]

Borylation of the lithium enolate exhibits unusual kinetics, being initially fast and then very slow. The unusually high stoichiometry of (*c*-Hex)$_2$BCl required to achieved full borylation of the lithium enolate suggested the formation of an initial product (perhaps similar to **28**) derived from [Li enolate + 2L$_2$BCl] that inhibits complete borylation (Scheme 3-3). Presumably, upon warming or addition of aldehyde, this initial product 'dissociates' to produce the (*E*)-enol borinate and (*c*-Hex)$_2$BCl.

In addition, experimental evidence also supported the formation of complex **32** from the enol borinate and lithium enolate (Scheme 3-3). At high temperature (>0 °C), the borate complex can undergo isomerization leading to the thermodynamically favoured (*Z*)-enol borinate. Reversible dissociation of the borate complex, a process that is facile even at low temperature (≤–42 °C), can exchange the geometries of the lithium enolate and enol borinate

Scheme 3-3. Proposed hypotheses for the highly selective formation of *anti* aldol product via lithiation/borylation of ethyl ketones.

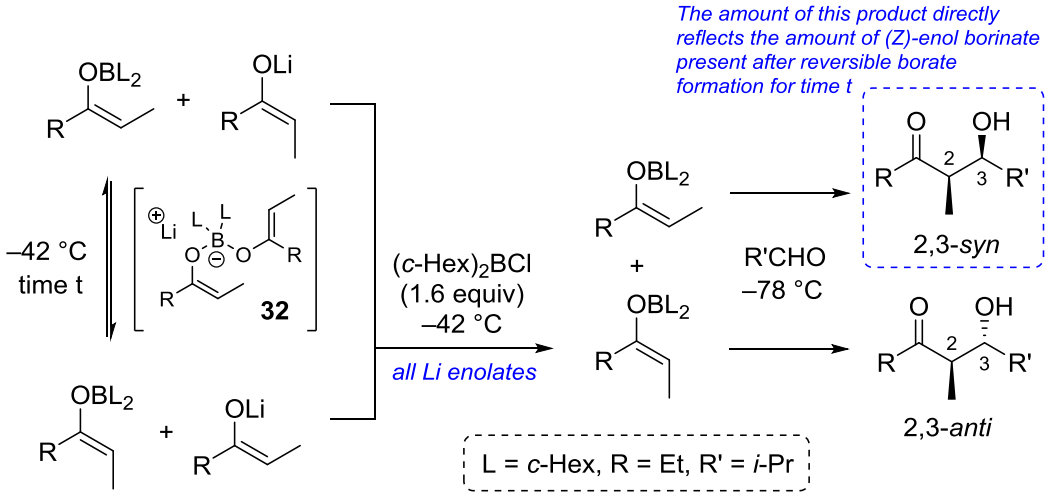


3.1 Future work

To clarify the role of the borate complex and the nature of the initial product **28** formed by the borylation of lithium enolate, the following experiments are proposed:

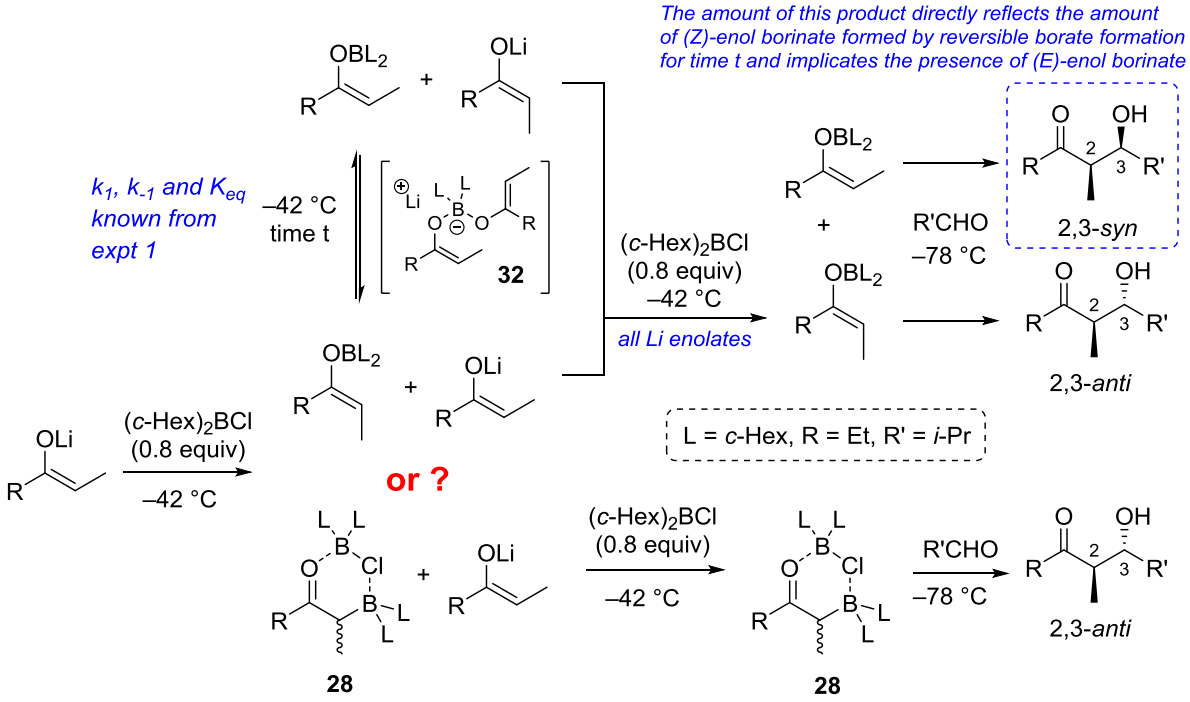
- Addition of (*E*)-enol borinate to lithium (*Z*)-enolate of 3-pentanone at –42 °C, followed after variable time by borylation with (*c*-Hex)$_2$BCl (1.6 equiv, with respect to the Li enolate) and aldolization with *i*-PrCHO. This experiment will reveal the rate that lithium enolate and enol borinate exchange geometries via reversible formation of the complex **32** and the resulting equilibrium mixture of enolates.

Scheme 3-4. Proposed experiment to reveal the rate that lithium enolate and enol borinate exchange geometries.



- Borylation of the lithium (*Z*)-enolate with (*c*-Hex)$_2$BCl (0.8 equiv, with respect to the Li enolate) at –42 °C, followed after variable time by borylation with an additional amount of (*c*-Hex)$_2$BCl (0.8 equiv), and aldolization with *i*-PrCHO (Scheme 3.5). Given the rate and equilibrium results from the above experiment, this experiment will reveal if the (*E*)-enol borinate is present prior to aldolization.

Scheme 3-5. Proposed experiment to reveal if the (*E*)-enol borinate is present prior to aldolization.



4 EXPERIMENTAL

4.1 General methods

Anhydrous solvents were distilled or prepared under Ar atmosphere as follows: tetrahydrofuran (THF) from benzophenone sodium ketyl; CH_2Cl_2 from CaH_2; hexane over sodium (Na) and stored over 4 Å molecular sieves; benzene, benzene-d_6, toluene-d_8 from freeze-pump-thaw cycles and stored under Ar over 3 Å molecular sieves. Unless otherwise noted, all experiments involving air- and/or moisture-sensitive compounds were conducted in an oven-dried round-bottom flask or 4 dram vial capped with a rubber septum and attached via a needle and connecting tubing to an Ar manifold equipped with mercury bubbler (ca. 5 mm positive pressure of Ar). Low temperature baths were ice/water (0 °C), CO_2(s)/CH_3CN (−42 °C), and CO_2(s)/acetone (−78 °C). Unless otherwise noted, reaction temperatures refer to that of the bath.

4.2 Spectral data

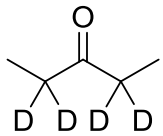
^1H, ^2H and ^{11}B NMR spectra were recorded on a 500 MHz Bruker Avance, a 500 MHz Bruker Avance III HD, or a 600 MHz Bruker Avance III HD NMR spectrometer at 25 °C in toluene-d_8, C_6D_6, or $CDCl_3$. The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), sep (septet), m (multiplet), br (broad), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. ^1H NMR spectra were normally obtained with a digital resolution of 0.244 Hz/pt (sweep width = 4000 Hz, FID = 32 K data points) and coupling constants are reported to the nearest 0.5 Hz. The ^1H NMR assignments were made on the basis of chemical shift, multiplicity, and consistency within a series of similar structures. Signals due to residual protonated solvent (^1H NMR) or deuterated solvent (^2H NMR) served as the internal standard: $CDCl_3$ (7.26 δ_H); C_6D_6 (7.16 δ_H); toluene-d_8 (7.09, 7.00, 6.98, 2.09 δ_H). ^{11}B chemical shifts were referenced using $BF_3.OEt_2$ as external standard.

4.3 Preparations of materials

(*c*-Hex)$_2$BCl was prepared by hydroboration of cyclohexene using $BH_2Cl.SMe_2$ according to Brown *et al.*,[37] purified by distillation under reduced pressure (bp 35-40 °C, 0.05 torr; ^{11}B NMR (hexane): δ 76 ppm), stored and used as 1.0 M solution in hexane under Ar. 9-BBN-Cl was synthesized by reaction of 9-BBN with PCl_5 in hexane according to Brown *et al.*,[38] purified by distillation under reduced pressure (bp 40-43 °C, 0.3 torr; ^{11}B NMR (hexane): δ 81 ppm), stored

and used as 0.80 M solution in hexane under Ar. (*c*-Hex)$_2$BOTf, 9-BBN-OTf (0.5 M in hexane), and Bu_2BOTf (1.0 M in CH_2Cl_2) were obtained from Sigma-Aldrich and used as received without further purification. *i*-PrCHO was freshly distilled from $CaCl_2$ under Ar before use. Benzaldehyde was distilled under reduced pressure and stored under Ar. 3-pentanone and 3-pentanone-d_4 were distilled under Ar from CaH_2 and stored over 3 Å molecular sieves. 2-methyl-3-pentanone and $(PhMe_2Si)_2NH$ from Aldrich were dried over 3 Å molecular sieves and used without further purification. Et_3N, *i*-Pr_2EtN (DIPEA), *i*-Pr_2NH (DIPA), *t*-$Bu(Me_3Si)NH$ and $(Me_3Si)_2NH$ (HMDS) were distilled under Ar from CaH_2 and stored under Ar over KOH (for non-silylated amines) or 3 Å molecular sieves (for silylated amines). *n*-Butylithium was titrated using 2,6-di-*tert*-butyl-4-methylphenol (BHT) as the titrant and fluorene as indicator. 2-(2-Ethyl-1,3-dioxolan-2-yl)propanol (precursor of aldehyde **38**) was prepared from ethyl propionate according to Ward *et al*.[35]

[2,2,4,4–$^2H_4$]pentan-3-one (3-pentanone-d_4)

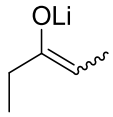


Following the procedure according to Nelsen *et al.*,[39] deuterium exchange was achieved by heating a mixture of 3-pentanone (30 mL, 0.28 mol), D_2O (9.0 mL, 0.45 mol), and K_2CO_3 (72 mg, 0.52 mmol) under reflux with stirring for 24 h. The bottom aqueous layer was removed and discarded and fresh D_2O/K_2CO_3 was added. After 5 exchanges, the organic layer was dried over Na_2SO_4 and distilled from CaH_2 under Ar to give 3-pentanone-d_4 (20 g, ca. 80% yield, 99% deuterium content by ^{1}H NMR).

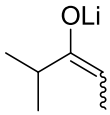
Solutions of lithium enolates of 3-pentanone, 3-pentanone-d_4 and 2-methyl-3-pentanone

To a Schlenk flask containing a stirring solution of HMDS (0.50 mL, 2.4 mmol) in THF (2.5 mL) under Ar at 0 °C was added *n*-BuLi (2.5 M in hexane; 0.80 mL, 2.0 mmol) dropwise. The mixture was stirred at 0 °C for 10 min and then cooled to –78 °C. The 'neat' ketone (2.0 mmol) was added dropwise to the lithium amide base and then continued stirring at –78 °C. After 30 min, the volatiles were removed under vacuum on a Schlenk line. The remaining solid was mainly lithium enolate, which was dissolved in C_6D_6 to make a stock solution and stored under Ar. The *E:Z* ratio of the enolate was determined by both ^{1}H NMR and from the *E:Z* ratio of the TMS enol

ethers obtained after quenching an aliquot from the stock solution with Me_3SiCl/Et_3N at –78 °C. The concentration of the stock solution was calibrated prior to use in further experiments by aldolization with benzaldehyde.

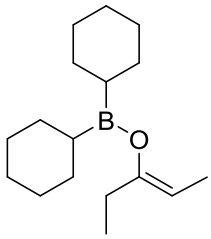


^{1}H NMR (C_6D_6, 600 MHz): δ 4.52 (br s, HC=COLi, *Z* isomer), 4.27 (br s, HC=COLi, *E* isomer), 2.28-2.21 (m, H_2CCH_3), 1.84-160 (m, H_3CCH), 1.22-1.14 (m, H_3CCH_2).



^{1}H NMR (Tol-d_8, 600 MHz): δ 4.27 (q, *J* = 6.0 Hz, HC=COLi, *E* isomer), 4.13 (q, *J* = 6.5 Hz, HC=COLi, *Z* isomer), 2.94 (sep, *J* = 7.0 Hz, $HC(CH_3)_2$, *E* isomer), 2.24 (sep, *J* = 6.5 Hz, $HC(CH_3)_2$, *Z* isomer), 1.83-1.67 (br, H_3CCH), 1.22 (d, *J* = 7.0, $2H_3CCH$, *Z* isomer), 1.16 (d, *J* = 7.0 $2H_3CCH$, *E* isomer).

Dicyclohexyl[(2*Z*)-pent-2-en-3-yloxy]borane [(*Z*)-19]

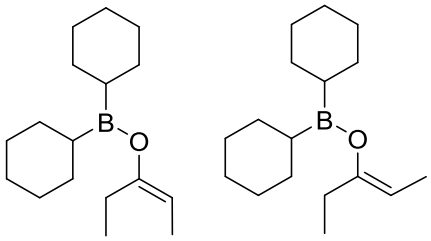


(*Z*)-**19**

Adapting the procedure from Brown,[40] DIPEA (0.30 mL, 1.7 mmol) and 3-pentanone (0.20 mL, 1.9 mmol) were sequentially added to a stirring solution of $(c\text{-Hex})_2BOTf$ (458.2 mg, 1.405 mmol) in hexane (5.0 mL) in a Schlenk flask under Ar at 0 °C. The mixture was stirred at 0 °C for 2 h (enolate formation was accompanied with formation of a white precipitate). The precipitate was filtered using Schlenk technique and the filtrate was concentrated under high vacuum. The residual yellowish oil (292.0 mg, ≤ 1.11 mmol) contained mainly (*Z*)-**19** (*E*:*Z* = 2:98 by ^{1}H NMR), and was dissolved in C_6D_6 to make a stock solution and stored under Ar. The concentration of the solution was calibrated prior to use by aldolization with excess benzaldehyde at –78 °C for 2 h. ^{1}H NMR (C_6D_6, 600 MHz): δ 4.57 (q, *J* = 6.5 Hz, HC=COB), 2.01 (q, *J* = 7.5 Hz, H_2CCH_3), 1.43 (d,

J = 6.5 Hz, H_3CCH=COB), 0.97 (t, J = 7.5 Hz, H_3CCH_2); ^{11}B NMR (C_6D_6, 600 MHz): δ 51.7 (br s).

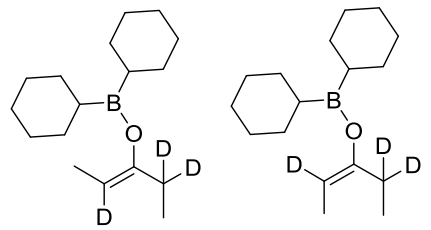
Dicyclohexyl(pent-2-en-3-yloxy)borane (*E*:*Z*, 56:44)



19

Adapting the procedure from Brown,[41] Et_3N (0.50 mL, 3.6 mmol) and 3-pentanone (0.44 mL, 4.2 mmol) were sequentially added to a stirring solution of (c-Hex)$_2$BCl (3.0 mL, 3.0 mmol, 1.0 M in hexane) in THF (9.0 mL) at 0 °C under Ar (enolate formation was accompanied with formation of ammonium salt as white precipitate). After 30 min, the precipitate was filtered using Schlenk technique and the filtrate was concentrated under high vacuum. Remaining yellowish oil (753.9 mg, ≤ 2.87 mmol) was a mixture of enol borinate **19** (Z:E = 39:61 by ^1H NMR) that was dissolved in C_6D_6 to make a stock solution and stored under Ar. The concentration of the solution was calibrated prior to use by aldolization with excess benzaldehyde at –78 °C for 2 h. ^1H NMR (C_6D_6, 600 MHz): Z isomer δ 4.58 (q, J = 6.5 Hz, HC=COB), 2.01 (q, J = 7.5 Hz, H_2CCH_3), 1.43 (d, J = 6.5 Hz, H_3CCH=COB), 0.97 (t, J = 7.5 Hz, H_3CCH_2); E isomer δ 4.67 (q, J = 7.0 Hz, HC=COB), 2.06 (q, J = 7.5 Hz, H_2CCH_3), 1.45 (d, J = 7.0 Hz, H_3CCH=COB), 0.98 (t, J = 7.5 Hz, H_3CCH_2); ^{11}B NMR (C_6D_6, 600 MHz): δ 51.4 (br s).

Dicyclohexyl([2,4,4–$^2H_3$]pent-2-en-3-yloxy)borane (23) (*E*:*Z*, 56:44)

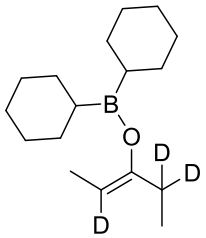


23

Similar to the above procedure for non-deuterated enol borinate, reaction 3-pentanone-d_4 (0.40 mL, 3.6 mmol) with (c-Hex)$_2$BCl and Et_3N gave the enol borinate as a clear colorless oil (634.6 mg, ≤ 2.39 mmol) that was a mixture of diastereomers (Z:E = 38:62 by both ^1H and ^2H NMR), that

was dissolved in C_6H_6 and stored as a stock solution. The concentration of the solution was calibrated prior to use by aldolization with excess benzaldehyde at –78 °C for 2 h. ^{1}H NMR (C_6D_6, 600 MHz): *Z* isomer δ 1.44 (br s, H_3CCD=COB), 0.96 (br s, H_3CCD_2); *E* isomer δ 1.43 (br s, H_3CCD=COB), 0.98 (br s, H_3CCD_2); ^{2}H NMR (C_6H_6, 600 MHz): *Z* isomer δ 4.57 (br s, DC=COB), 1.94 (br s, D_2CCH_3); *E* isomer δ 4.68 (br s, DC=COB), 2.00 (br s, D_2CCH_3); ^{11}B NMR (C_6D_6, 600 MHz): δ 51.4 (br s).

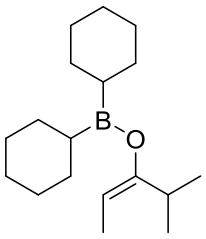
Dicyclohexyl[(2*Z*)-[2,4,4–^{2}H$_3$]pent-2-en-3-yloxy]borane [(*Z*)-23]



(*Z*)-**23**

To a solution of the deuterated boron enolate mixtures above (0.67 M in C_6H_6; 2.0 mL; 1.3 mmol) in Schlenk flask under Ar at rt was added the lithium enolate of 3-pentanone-d_4 (1.0 M in C_6H_6; 1.0 mL, 1.0 mmol). The mixture was kept under Ar and stirred at rt for 16 h. An aliquot from the reaction mixture showed completed isomerization by ^{1}H NMR. Excess Me_3SiCl/Et_3N was added and, after 15 min, the volatiles were removed under high vacuum on a Schlenk line. The residual oil was mainly (*Z*)-**23** (*Z*:*E* = 93:7 by ^{1}H and ^{2}H NMR), that was dissolved in C_6D_6 to make a stock solution and stored under Ar. The concentration of the solution was calibrated prior to use by aldolization with excess benzaldehyde at –78 °C for 2 h. ^{1}H NMR (C_6D_6, 600 MHz): δ 1.44 (br s, H_3CCD=COB), 0.96 (br s, H_3CCD_2); ^{2}H NMR (C_6H_6, 600 MHz): δ 4.57 (br s, DC=COB), 1.94 (br s, D_2CCH_3); ^{11}B NMR (C_6D_6, 600 MHz): δ 51.7 (br s).

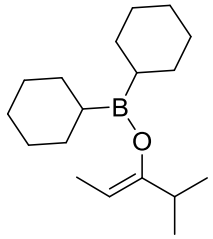
Dicyclohexyl[(2*E*)-4-methylpent-2-en-3-yloxy]borane [(*E*)-21]



(*E*)-**21**

Et_3N (0.60 mL, 4.0 mmol) and 2-methyl-3-pentanone (0.50 mL, 3.9 mmol) were sequentially added to a stirring solution of (*c*-Hex)$_2$BCl (3.0 mL, 3.0 mmol, 1.0 M in hexane) in THF (9.0 mL) at 0 °C under Ar (enolate formation was accompanied with formation of a white precipitate). After 1.5 h, the precipitate was filtered using Schlenk technique and the filtrate was concentrated under high vacuum on a Schlenk line. The residual yellowish oil (728.4 mg, ≤ 2.6 mmol) was mainly (*E*)-**21** (E:Z = 97:3 by ^{1}H NMR), that was dissolved in C_6H_6 to make a stock solution and stored under Ar. The concentration of the solution was calibrated prior to use by aldolization with excess benzaldehyde. ^{1}H NMR (C_6D_6, 600 MHz): δ 4.58 (q, *J* = 7.0 Hz, HC=COB), 2.71 (sep, *J* = 7.0 Hz, HC(CH$_3$)$_2$), 1.47 (d, *J* = 7.0 Hz, H$_3$CCH=COB), 1.00 (t, *J* = 7.0 Hz, 2H$_3$CCH), ^{11}B NMR (C_6D_6, 600 MHz): δ 51.2 (br s).

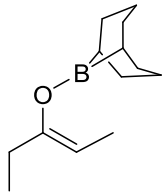
Dicyclohexyl[(2*Z*)-4-methylpent-2-en-3-yloxy]borane [(*Z*)-21]



(*Z*)-**21**

To a stirring solution of (*E*)-**21** (0.20 M in C_6H_6; 5.0 mL, 1.0 mmol) in Schlenk flask under Ar at rt was added the lithium enolate of 2-methyl-3-pentanone (1.0 M in C_6H_6; 1.00 mL, 1.00 mmol). The mixture was kept under Ar and stirred at rt for 16 h. An aliquot from the reaction mixture showed completed isomerization by ^{1}H NMR. Excess Me_3SiCl/Et_3N was added and, after 15 min, the volatiles were removed under high vacuum on a Schlenk line. The residual yellowish oil was mainly (*Z*)-**21** (*Z*:*E* = 93:7 by ^{1}H NMR), that was dissolved in C_6D_6 to make a stock solution and stored under Ar. The concentration of the solution was calibrated prior to use by aldolization with excess benzaldehyde. ^{1}H NMR (C_6D_6, 600 MHz): δ 4.61 (q, *J* = 6.5 Hz, HC=COB), 2.18 (sep, *J* = 7.0 Hz, HC(CH$_3$)$_2$), 1.43 (d, *J* = 7.0 Hz, H$_3$CCH=COB), 1.03 (t, *J* = 7.0 Hz, 2H$_3$CCH), ^{11}B NMR (C_6D_6, 600 MHz): δ 51.7 (br s).

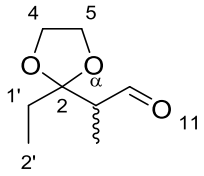
9-[[(1*Z*)-1-Ethyl-1-propen-1-yl]oxy]-9-borabicyclo[3.3.1]nonane



(*Z*)-**20**

Adapting the procedure from Brown,[40] DIPEA (0.70 mL, 4.2 mmol) and 3-pentanone (0.40 mL, 3.8 mmol) were sequentially added to a stirring solution of 9-BBNOTf in hexane (0.5 M, 6.0 mL, 3.0 mmol) under Ar at 0 °C (enolate formation was accompanied with formation of a white precipitate). After 2 h, the precipitate was filtered using Schlenk technique and the filtrate was concentrated under high vacuum on a Schlenk line. The residual yellowish oil (292.0 mg, ≤ 1.11 mmol) was exclusively (*Z*)-**20** (*Z*:*E* = 100:0 by ^{1}H NMR), that was dissolved in C_6D_6 to make a stock solution and stored under Ar. The concentration of the solution was calibrated prior to use by aldolization with excess benzaldehyde. ^{1}H NMR (C_6D_6, 600 MHz): δ 4.62 (q, *J* = 6.5 Hz, HC=COB), 2.04 (q, *J* = 7.5 Hz, H_2CCH_3), 1.51 (d, *J* = 6.5 Hz, H_3CCH=COB), 0.97 (t, *J* = 7.5 Hz, H_3CCH_2); ^{11}B NMR (C_6D_6, 600 MHz): δ 56.9 (br s).

2-(2-Ethyl-1,3-dioxolan-2-yl)propanal [(±)-38]

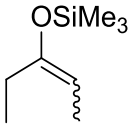


(±)-**38**

Adapting the procedure of Stahl,[42] a solution of ABNO (7.0 mg, 0.05 mmol, 0.005 equiv) in CH_3CN (1 mL), a solution of CuI (95 mg, 0.5 mmol, 0.05 equiv) in CH_3CN (10 mL) and NMI (80 μL, 1 mmol, 0.1 equiv) were added to a solution of 2-(2-ethyl-1,3-dioxolan-2-yl)propanal (1.6 g, ≤ 10 mmol, 1 equiv) in CH_3CN (14 mL) in a 25 × 150 mm test tube with an oval stir bar. The vessel was fitted with a rubber septum with a hole in the center holding an glass gas dispersion tube (7 mm × 210 mm, 4−8 μm porosity) attached to a compressed air line. Air was bubbled into the reaction mixture through the dispersion tube and the reaction was stirred at 700 rpm at room temperature. After 3 h, the reaction mxture was transferred to a separatory funnel, diluted with water (100 mL), and extracted with pentane (3 x 80 mL). The combined organic layers were washed sequentially with 10% aq. $Na_2S_2O_3$ (100 mL) (to remove pink color of iodine), and brine

(100 mL), dried over Na_2SO_4, and concentrated to afford the known[43] aldehyde (±)-**38** as a colorless oil (1.56 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.80 (1H, d, *J* = 2 Hz, CHO), 4.08-4.00 (4H, m, H_2CO ×2), 2.74 (1H, dq, *J* = 2, 7 Hz, HC-α), 1.74 (1H, dq, *J* = 7.5, 14.5 Hz, HC-1'), 1.62 (1H, dq, *J* = 7.5, 14.5 Hz, HC-1'), 1.13 (3H, d, *J* = 7 Hz, H_3CC-α), 0.93 (3H, t, *J* = 7.5 Hz, H_3C-2').

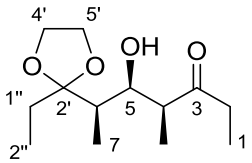
Trimethyl(pent-2-en-3-yloxy)silane (14)



14

Adapting the procedure of Iqbal,[44] commercially available anhydrous DMF (200 mL) was added to a flask containing dry NaBr (19.6 g, 0.190 mol) under Ar. After 30 min of stirring, the solid had dissolved, and freshly distilled Me_3SiCl (24 mL, 21 g, 0.19 mol) was added. After 30 min (the mixture had become milky white), 3-pentanone (13 mL, 11 g, 0.12 mol) and Et_3N (27 mL, 20 g, 0.19 mol) were sequentially added. The reaction was monitored by ^{1}H NMR of small aliquots and, after 5 days, had reached 90% conversion. The mixture was extracted with pentane, and the combined extracts were washed sequentially with saturated aq $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and subjected to fractional distillation. After the pentane was removed, a small fraction (2.4 g) was obtained at 90−105 °C that was a ca. 6:1 mixture of **14** and Et_3N, respectively (by ^{1}H NMR). The remaining yellow oil was **14** as a 3:1 mixture of *Z*:*E* diastereomers (14.6 g, 76%) (cf. a 95:5 mixture (83%) in ref 44).

(4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methylheptan-3-one (40)

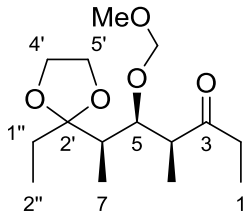


(±)-**40**

According to a known procedure from Ward *et al.*,[35] $BF_3{\cdot}OEt_2$ (0.43 mL, 0.49 g, 3.5 mmol) was added dropwise via a syringe over 5 min to a stirred solution of crude (±)-**38** (555 mg, ≤3.51 mmol) and **14** (*Z*:*E*, 3.3:1; 1.4 mL, 1.1 g, 7.0 mmol) in CH_2Cl_2 (55 mL) at −78 °C under Ar. After 10 min, the reaction was quenched by addition of saturated aq NH_4Cl (5 mL), and after warming to ambient temperature, the mixture was extracted with CH_2Cl_2. The combined organic layers were

dried over Na_2SO_4 and concentrated to obtain the crude product whose ^1H NMR indicated the presence of a 9:1 mixture of **40** and its C-4 isomer, respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) gave a 2:1 mixture of **40** and its C-4 isomer, respectively (125 mg, 15%), and **40** (432 mg, 51%): colorless oil, ^1H NMR ($CDCl_3$) δ 4.09 (1H, d, J = 9 Hz, HC-5), 4.03−3.92 (4H, m, H_2C-4′, H_2C-5′), 3.10 (1H, br s, HO), 2.78 (1H, dq, J = 9, 7 Hz, HC-4), 2.54 (1H, dq, J = 18, 7 Hz, H_2C-2), 2.41 (1H, dq, J = 18, 7 Hz, H_2C-2), 1.81 (1H, dq, J = 1, 7 Hz, HC-6), 1.68 (2H, ap q, J = 7.5 Hz, H_2C-1″), 1.21 (3H, d, J = 7 Hz, H_3CC-4), 1.03 (3H, t, J = 7 Hz, H_3C-1), 0.93 (3H, d, J = 7 Hz, H_3C-7), 0.86 (3H, t, J = 7.5 Hz, H_3C-2″).

(4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-methoxymethoxy-4-methyl heptan-3-one (29).



(±)-**29**

According to known procedure from Ward *et al.*,[35] *i*-Pr_2EtN (1.1 mL, 0.82 g, 6.3 mmol) and MOMCl (0.20 mL, 0.21 g, 2.6 mmol) was subsequently added to a solution of **40** (430 mg, 1.75 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C under Ar. The solution was warmed up to rt and stirring continued for 6 h. A second portion of MOMCl (0.20 mL, 0.21 g, 2.6 mmol) was added to the solution at rt and stirring continued overnight. After completion (21 h total), reaction mixture was quenched with addition of 4% aq. HCl and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated to obtain the crude product. Fractionation of the crude product by FCC (20 % ethyl acetate in hexane) afforded the titled compound (498 mg, 99%): colorless oil, TLC R_f = 0.4 (40% ethyl acetate in hexane); ^1H NMR ($CDCl_3$) δ 4.68 (1H, d, J = 6.5 Hz, HCO_2), 4.54 (1H, d, J = 6.5 Hz, HCO_2), 3.97 (1H, dd, J = 3, 5 Hz, HC-5), 3.95−3.90 (4H, m, H_2C-4′, H_2C-5′), 3.32 (3H, s, H_3CO), 2.81 (1H, dq, J = 5, 7 Hz, HC-4), 2.65 (1H, dq, J = 18, 7 Hz, H_2C-2), 2.44 (1H, dq, J = 18, 7 Hz, H_2C-2), 1.91 (1H, dq, J = 3, 7 Hz, HC-6), 1.69−1.57 (2H, m, H_2C-1″), 1.06 (3H, d, J = 7 Hz, H_3CC-4), 1.01 (3H, t, J = 7 Hz, H_3C-1), 0.87 (3H, d, J = 7 Hz, H_3C-7), 0.83 (3H, t, J = 7.5 Hz, H_3C-2″).

4.4 General procedures for Schemes and Tables

Table 2-1

A representative procedure is shown. Entry 3: A solution of $LiN(SiMe_2Ph)_2$ was prepared by addition of *n*-BuLi (2.5 M in hexane; 0.10 mL, 0.25 mmol) to a stirring solution of $(PhMe_2Si)_2NH$ (75 μL, 0.26 mmol) in THF (1.0 mL) at 0 °C under Ar. After 10 min, the above solution was cooled to −78 °C and a solution of 3-pentanone (21 μL, 0.20 mmol) in THF (0.95 M) was added dropwise. After 30 min, Li enolate formation was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether in >90% yield). (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.32 mL, 0.32 mmol) was added rapidly (<1 min) at –78 °C and, after 5 min, the solution was continued stirring at –42 °C for 2 h. After cooling to –78 °C, *i*-PrCHO (0.10 mL, 1.0 mmol) was added rapidly (<30 s) via a syringe to the stirring solution under Ar. After completion (2 h), the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR. The yield of aldol adducts (>95%) was determined by ^{1}H NMR using trichloroethylene as the internal standard.

Scheme 2-1

A solution of $LiN(SiMe_3)_2$ was prepared by addition of *n*-BuLi (2.5 M in hexane; 0.10 mL, 0.25 mmol) to a stirring solution of $(Me_3Si)_2NH$ (54 μL, 0.26 mmol) in THF (1.0 mL) at 0 °C under Ar. After 10 min, the above solution was cooled to −78 °C and a solution of 3-pentanone (21 μL, 0.20 mmol) in THF (0.95 M) was added dropwise. After 30 min, Li enolate formation was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether in >90% yield). (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.32 mL, 0.32 mmol) was added rapidly (<1 min) at –78 °C and the solution was continued stirring for 0.5 h. The volatiles was removed under vacuum on a Schlenk line at room temperature. The residual oil was predominantly (*E*)-**19** (*E*:*Z* = 98:2, by ^{1}H NMR in C_6D_6). A parallel reaction was done with identical enolization and borylation conditions, followed by aldolization with *i*-PrCHO (0.10 mL, 1.0 mmol) at –78 °C in 2 h, giving crude product containing a >19:1 mixture of **15a**:**15s**.

Scheme 2-2

A solution of MeLi (1.65 M in Et_2O; 0.18 mL, 0.30 mmol) was added via a syringe to a stirring solution of TMS enol ether **14** (*E*:*Z*, 25:75; 47 mg, 0.3 mmol) in THF (ca. 0.2 M) at 0 °C under Ar. After 1 h, Li enolate formation was deemed complete (at this stage, aldolization with *i*-PrCHO at –42 °C for 3 min gave aldol products **15a**:**15s** = 30:70 in >90% yield). (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.48 mL, 0.48 mmol) was added at –78 °C and stirring continued at –42 °C for 1 h. After cooling to –78 °C, *i*-PrCHO (0.14 mL, 1.5 mmol) was added rapidly (<30 s) via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR. The yield of aldol adducts (90%) was determined by ^{1}H NMR using trichloroethylene as the internal standard.

Table 2-2

Li phenolate (1.0 M in C_6D_6; 0.10 mL, 0.1 mmol) was added to enol borinate **19** (*E*:*Z* = 56:44, 1.0 M in C_6D_6; 0.30 mL, 0.30 mmol) in an NMR tube at room temperature under Ar. The NMR tube was then capped and sealed under Ar for monitoring by ^{1}H NMR. After 11 h, an *E*:*Z* = 7:93 ratio was reached that remained unchanged after an additional 6 h.

Table 2-3

A representative procedure is shown. Entry 1: Freshly prepared Li phenolate (0.46 M in THF; 0.13 mL, 0.060 mmol) was added to enol borinate **19** (*E*:*Z* = 56:44, 1.0 M in C_6D_6; 0.20 mL, 0.20 mmol) in THF (0.30 mL) at rt under Ar. After stirring for 2 h, the reaction mixture was cooled to –78 °C and *i*-PrCHO (0.10 mL, 1.0 mmol) was added rapidly (<30 s) via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was

analyzed by ^{1}H NMR. The yield of aldol adducts (90%) was determined by ^{1}H NMR using trichloroethylene as the internal standard.

Table 2-4

Li enolate of 3-pentanone (*E*:*Z* = 30:70, 1.0 M in C_6D_6; 0.10 mL, 0.1 mmol), and degassed C_6D_6 (0.10 mL) was added to **19** (*E*:*Z* = 56:44, 1.0 M in C_6D_6; 0.20 mL, 0.20 mmol) in an NMR tube at room temperature under Ar. The NMR tube was then capped and sealed under Ar for monitoring by ^{1}H NMR (entries 1-3). After 1.5 h, an *E*:*Z* = 7:93 ratio was reached and remained unchanged after an additional 14 h. For ^{1}H NMR measurement at –42 °C (entry 4), toluene-d_8 was used instead of C_6D_6.

Scheme 2-3

Li enolate of 3-pentanone (*E*:*Z* = 30:70, 1.0 M in C_6D_6; 0.10 mL, 0.1 mmol), and degassed C_6D_6 (0.20 mL) was added to (*Z*)-enol borinate **20** (*E*:*Z* = 0:100, 1.0 M in C_6D_6; 0.10 mL, 0.10 mmol) in an NMR tube at room temperature under Ar. The NMR tube was then capped and sealed under Ar for monitoring by ^{1}H NMR overtime. After 4 h, an *E*:*Z* = 10:90 ratio was reached and remained unchanged after an additional 24 h.

Scheme 2-4

Li enolate of 2-methyl-3-pentanone (*E*:*Z* = 13:87, 1.0 M in tol-d_8; 0.10 mL, 0.1 mmol) was added to the (*E*)-enol borinate **21** (*E*:*Z* = 95:5, 0.9 M in tol-d_8; 0.10 mL, 0.090 mmol) in C_6D_6 (0.20 mL) in an NMR tube at room temperature under Ar. The NMR tube was then capped and sealed under Ar for monitoring by ^{1}H NMR overtime. After 16 h, an *E*:*Z* = 7:93 ratio was reached and remained unchanged after an additional 24 h.

Table 2-5

A representative procedure is shown. Entry 3: To a stirring solution of **19** (*E*:*Z* = 56:44; 1.0 mL, 0.20 mmol) in THF (0.2 M) at –42 °C was added HMDS (42 μL, 0.20 mmol). After 2 h, the mixture was cooled to –78 °C and *i*-PrCHO (0.10 mL, 1.0 mmol) was added rapidly (<30 s) via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and

30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR. For entries 5-12, (*c*-Hex)$_2$BCl (1.0 M in hexane, 0.20 mL, 0.20 mmol) and LiCl (0.5 M in THF, 0.40 mL, 0.20 mmol) were used as the additives.

Scheme 2-5

a) A solution of LiN(SiMe$_2$Ph)$_2$ was prepared by addition of *n*-BuLi (2.5 M in hexane; 50 μL, 0.12 mmol) to a stirring solution of (PhMe$_2$Si)$_2$NH (38 μL, 0.13 mmol) in THF (0.50 mL) at 0 °C under Ar. After 10 min, the above solution was cooled down to −78 °C and a solution of 3-pentanone (11 μL, 0.10 mmol) in THF (0.95 M) was added dropwise to the lithium amide base. After 30 min, Li enolate formation was deemed complete (quenching the reaction with Me$_3$SiCl/Et$_3$N at this stage gave the corresponding trimethylsilyl enol ether *E*:*Z* = 0:100 in >90% yield). (*Z)*-enol borinate (0.60 M in C_6D_6; 0.10 mL, 0.060 mmol) was added at −78 °C, followed by (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.16 mL, 0.16 mmol), and stirring continued at –78 °C for 30 min. PhCHO (50 μL, 0.50 mmol) was added rapidly (<30 s) via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR. The yield of aldol adducts (94%) was determined by ^{1}H NMR using trichloroethylene as the internal standard.

b) A solution of LiN(TMS)*t*-Bu was prepared by addition of *n*-BuLi (2.5 M in hexane; 50 μL, 0.12 mmol) to a stirring solution of *t*-Bu(TMS)NH (25 μL, 0.13 mmol) in THF (0.50 mL) at 0 °C under Ar. After 10 min, the ice bath was removed and a solution of 3-pentanone (11 μL, 0.10 mmol) in THF (0.95 M) was added dropwise into the lithium amide base. After 15 min, Li enolate formation was deemed complete (quenching the reaction with Me$_3$SiCl/Et$_3$N at this stage gave the corresponding trimethylsilyl enol ether *E*:*Z* = 97:3 in >90% yield) and the mixture was cooled to −78 °C. (*Z*)-**19** (0.60 M in C_6D_6; 0.17 mL, 0.10 mmol) and (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.16 mL, 0.16 mmol) was added sequentially to the stirring solution. After 30 min, PhCHO (50 μL,

0.50 mmol) was added rapidly (<30 s) via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR. The yield of aldol adducts (>99%) was determined by ^{1}H NMR using trichloroethylene as the internal standard.

Scheme 2-6

a) To a NMR tube containing a mixture of (*Z*)-enol borinate **21** (0.80 M in tol-d_8; 0.10 mL, 0.080 mmol) and lithium (*Z)*-enolate (*Z*:*E* = 90:10, 1.0 M in tol-d_8; 0.10 mL, 0.10 mmol) in tol-d_8 (0.20 mL) at –42 °C was added (*c*-Hex)$_2$BCl (1.0 M in tol-d_8; 0.50 mL, 0.50 mmol). After 1 h, ^{1}H NMR of the mixture was obtained at –40 °C and at rt to determine *E*:*Z* enol borinate.

b) A solution of LiN(TMS)*t*-Bu was prepared by addition of *n*-BuLi (2.5 M in hexane; 50 µL, 0.12 mmol) to a stirring solution of *t*-Bu(TMS)NH (25 µL, 0.13 mmol) in THF (0.50 mL) at 0 °C under Ar. After 10 min, the ice bath was removed and a solution of 2-methyl-3-pentanone (12 µL, 0.096 mmol) in THF (0.80 M) was added dropwise into the lithium amide base. After 15 min, Li enolate formation was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether *E*:*Z* = 94:6 in >90% yield) and the mixture was cooled to −78 °C. (*Z*)-enol borinate **21** (0.65 M in C_6D_6; 0.16 mL, 0.10 mmol) and (*c*-Hex)$_2$BCl (2.0 M in hexane; 0.25 mL, 0.50 mmol) were added sequentially to the stirring solution at –42 °C. After 1 h, PhCHO (50 µL, 0.50 mmol) was added rapidly at −78 °C (<30 s) via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR. The yield of aldol adducts (>99%) was determined by ^{1}H NMR using trichloroethylene as the internal standard.

Table 2-6

A representative procedure is shown. Entry 1: A solution of $LiN(SiMe_2Ph)_2$ was prepared by addition of *n*-BuLi (2.5 M in hexane; 0.10 mL, 0.25 mmol) to a stirring solution of $(PhMe_2Si)_2NH$ (75 µL, 0.26 mmol) in THF (1.0 mL) at 0 °C under Ar. After 10 min, the above solution was cooled down to −78 °C and a solution of 3-pentanone (21 µL, 0.20 mmol) in THF (0.95 M) was added dropwise into the lithium amide base. After 30 min, Li enolate formation was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether *Z*:*E* = 100:0 in >90% yield). $(c\text{-Hex})_2BCl$ (1.0 M in hexane; 0.32 mL, 0.32 mmol) was added and stirring continued at –78 °C for 5 min. *i*-PrCHO (0.10 mL, 1.0 mmol) was added rapidly (<30 s) at –78 °C via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR. The yield of aldol adducts (>95%) was determined by ^1H NMR using trichloroethylene as the internal standard.

Scheme 2-7

A solution of $LiN(SiMe_2Ph)_2$ was prepared by addition of *n*-BuLi (2.5 M in hexane; 50 µL, 0.12 mmol) to a stirring solution of $(PhMe_2Si)_2NH$ (38 µL, 0.13 mmol) in THF (0.50 mL) at 0 °C under Ar. After 10 min, the above solution was cooled to −78 °C and a solution of 3-pentanone (11 µL, 0.10 mmol) in THF (0.95 M) was added dropwise to the lithium amide base. After 30 min, the formation of Li enolate **22** was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether *Z*:*E* = 100:0 in >90% yield). Deuterated (*Z*)-enol borinate **23** (1.0 M in C_6D_6; 0.10 mL, 0.10 mmol) was added and stirring continued at –42 °C for the indicated time, followed by addition of excess Me_3SiCl/Et_3N at –42 °C. After 15 min, the mixture was then warmed to rt, and the volatiles were removed under vacuum (0.06 torr) on a Schlenk line. Deuterium distribution was determined by ^1H NMR analysis of the residual colorless oil in C_6D_6.

Table 2-7

A representative procedure is shown. Entry 1: A solution of $LiN(SiMe_3)_2$ was prepared by addition of *n*-BuLi (2.5 M in hexane; 0.10 mL, 0.25 mmol) to a stirring solution of $(Me_3Si)_2NH$ (56 μL, 0.27 mmol) in THF (1.0 mL) at 0 °C under Ar. After 10 min, the above solution was cooled to −78 °C and a solution of 2-methyl-3-pentanone (25 μL, 0.20 mmol) in THF (0.8 M) was added dropwise to the lithium amide base. After 1 h, Li enolate formation was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether *Z*:*E* = 97:3 in >90% yield). $(c\text{-Hex})_2BCl$ (1.0 M in hexane; 0.32 mL, 0.32 mmol) was added and stirring continued at –78 °C. After 5 min, PhCHO (40 μL, 0.40 mmol) was added rapidly (<30 s) at –78 °C via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR. The yield of aldol adducts (89%) was determined by ^1H NMR using trichloroethylene as the internal standard.

Table 2-8

A representative procedure is shown. Entry 1: A solution of $LiN(SiMe_3)_2$ was prepared by addition of *n*-BuLi (2.5 M in hexane; 50 μL, 0.12 mmol) to a stirring solution of $(Me_3Si)_2NH$ (28 μL, 0.13 mmol) in THF (0.50 mL) at 0 °C under Ar (in cases with a lower concentration, a higher amount of THF was utilized at this stage). After 10 min, the above solution was cooled to −42 °C and a solution of **29** (30 mg, 0.10 mmol) in THF (0.2 M) was added dropwise to the lithium amide base. After 1 h, Li enolate formation was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether *Z*:*E* = 15:1 in >90% yield). $(c\text{-Hex})_2BCl$ (1.0 M in hexane; 0.16 mL, 0.16 mmol) was added and stirring continued at –78 °C. After 5 min. *i*-PrCHO (50 μL, 0.55 mmol) was added rapidly (<30 s) at –78 °C via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with

CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR.

Table 2-9

A representative procedure is shown. Entry 1: A solution of $LiN(SiMe_3)_2$ was prepared by addition of *n*-BuLi (2.5 M in hexane; 50 µL, 0.12 mmol) to a stirring solution of $(Me_3Si)_2NH$ (28 µL, 0.13 mmol) in THF (0.50 mL) at 0 °C under Ar. After 10 min, the above solution was cooled to −42 °C and a solution of **29** (30 mg, 0.10 mmol) in THF (0.2 M) was added dropwise to the lithium amide base. After 1 h, Li enolate formation was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether *Z*:*E* = 15:1 in >90% yield). $(c\text{-Hex})_2BCl$ (1.0 M in hexane; 0.16 mL, 0.16 mmol) was added and stirring continued at –78 °C. After 5 min. *i*-PrCHO (50 µL, 0.55 mmol) was added rapidly (<30 s) at –78 °C via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR.

Table 2-10

Entry 1: To a stirring solution of enol borinate **19** (*E*:*Z* = 73:27; 0.28 M, 0.80 mL, 0.23 mmol) in THF, prepared by a general soft enolization procedure of 3-pentanone **13** using $(c\text{-Hex})_2BCl/Et_3N$ in Et_2O at 0 °C for 0.5 h,[41] was added *i*-PrCHO (5.0 µL, 0.055 mmol) rapidly (<30 s) at –78 °C via a syringe under Ar. After completion (2 h), the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to yield a 50:1 mixture of crude products **15a** and **15s** (by ^1H NMR). The yield of aldol adducts (97% with respect to the aldehyde) was determined by ^1H NMR using trichloroethylene as the internal standard.

Entry 2: To a stirring solution of enol borinate **19** (*E*:*Z* = 63:37; 0.26 M in THF, 0.30 mL, 0.23 mmol) (prepared by soft enolization of 3-pentanone **13** using (*c*-Hex)$_2$BCl/Et$_3$N in THF at 0 °C for 0.5 h)[41] at –78 °C under Ar was added (±)-**38** (0.26 M in THF, 0.10 mL, 0.026 mmol) rapidly (<30 s) via syringe. After 18 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to yield the crude product that was a 30:1 mixture of known[35] products (±)-**39sa** and (±)-**39ss** (by ^{1}H NMR). The yield of aldol adducts (92% with respect to **38**) was determined by ^{1}H NMR using trichloroethylene as the internal standard.

Table 2-11

A general procedure is shown: A solution of lithium amide was prepared by addition of *n*-BuLi (2.5 M in hexane; 50 mL, 0.12 mmol) to a stirring solution of corresponding secondary amine (0.13 mmol) in THF (0.50 mL) at 0 °C under Ar. After 10 min, the above solution was cooled to −78 °C and a solution of 3-pentanone (11 µL, 0.10 mmol) in THF (0.95 M) was added dropwise into the lithium amide base. After 30 min, Li enolate formation was deemed complete (quenching the reaction with Me$_3$SiCl/Et$_3$N at this stage gave the corresponding trimethylsilyl enol ether in >90% yield). (*c*-Hex)$_2$BX solution [(*c*-Hex)$_2$BCl, 1.0 M in hexane; (*c*-Hex)$_2$BOTf, 0.80 M in hexane] was added at –78 °C and, after 5 min, stirring continued at –42 °C. After 2 h (removal of the volatiles under vacuum at –42 °C at this stage gave the enol borinate mixture which was analyzed by ^{1}H NMR at –42 °C in toluene-d$_8$), *i*-PrCHO (0.10 mL, 1.0 mmol) was added rapidly (<30 s) via a syringe to the stirring solution at –78 °C under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR. The yield of aldol adducts (95%) was determined by ^{1}H NMR using trichloroethylene as the internal standard.

Table 2-12

A representative procedure is shown. Entry 2: To a stirring solution of **19** (*E*:*Z* = 73:27; 0.90 mL, 0.15 mmol) in THF (0.17 M) at –42 °C under Ar was added (*c*-Hex)$_2$BOTf (0.6 M in hexane; 0.10 mL, 0.060 mmol). The reaction was stirred at –42 °C for 2 h. After cooling to –78 °C, *i*-PrCHO (0.10 mL, 1.0 mmol) was added rapidly (<30 s) via a syringe to the stirring solution under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR.

Table 2-13

A general procedure is shown. A solution of lithium amide was prepared by addition of *n*-BuLi (2.5 M in hexane; 50 mL, 0.12 mmol) to a stirring solution of corresponding secondary amine (0.13 mmol) in THF (0.50 mL) at 0 °C under Ar. After 10 min, the above solution was cooled to −78 °C and a solution of 3-pentanone (11 μL, 0.10 mmol) in THF (0.95 M) was added dropwise to the lithium amide base. After 30 min, Li enolate formation was deemed complete (quenching the reaction with Me_3SiCl/Et_3N at this stage gave the corresponding trimethylsilyl enol ether in >90% yield). L_2BX solution (Bu_2BOTf, 1.0 M in CH_2Cl_2; 9-BBNOTf, 0.50 M in hexane; 9-BBN-Cl, 0.80 M in hexane; 0.16 mmol) was added at –78 °C and, after 5 min, stirring continued at –42 °C. After 2 h (removal of the volatiles under vacuum at –42 °C at this stage gave the boron enolate mixture which was analyzed by ^{1}H NMR at –42 °C in toluene-d_8), *i*-PrCHO (0.10 mL, 1.0 mmol) was added rapidly (<30 s) via a syringe to the stirring solution at –78 °C under Ar. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR. The yield of aldol adducts was determined by ^{1}H NMR using trichloroethylene as the internal standard.

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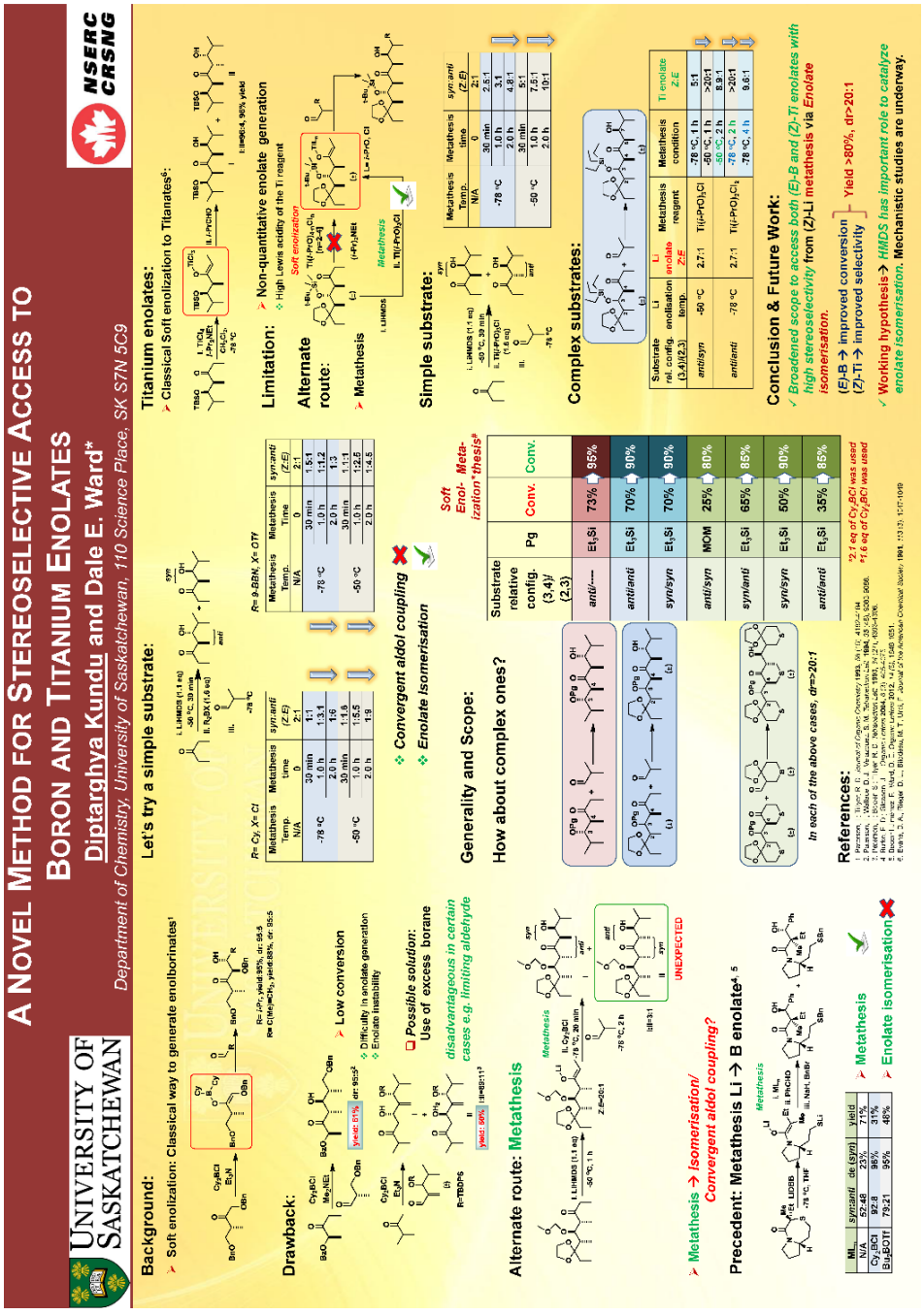
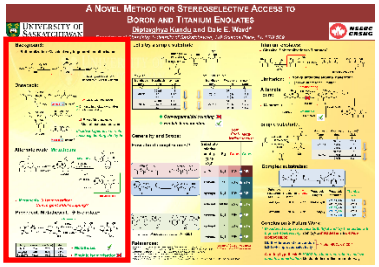
Appendix

POSTER PRESENTATIONS BY D. KUNDU

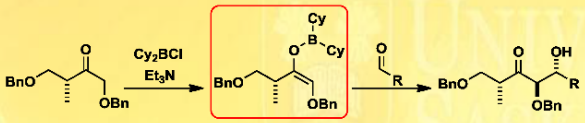
29. Kundu, D.; Ward, D. E., A Novel Method for Stereoselective Access to Boron and Titanium Enolates. Presented at the 6th Banff Symposium on Organic Chemistry, Banff, Alberta, Canada, November 8–11, 2013.



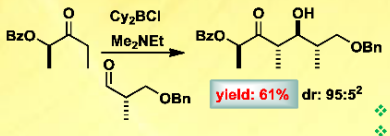


Background:

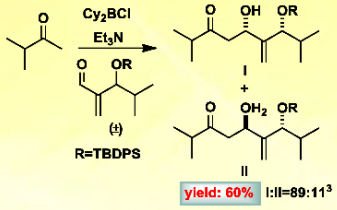
- Soft enolization: Classical way to generate enolborinates[1]



Drawback:



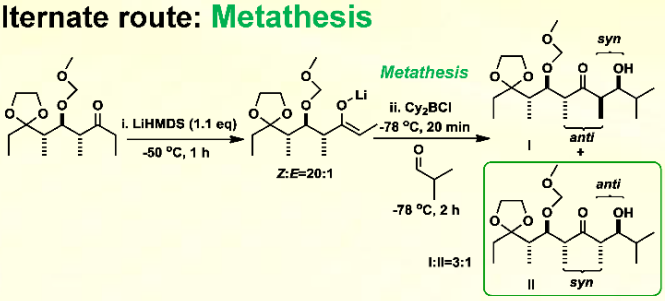
- Low conversion
  - Difficulty in enolate generation
  - Enolate instability



- ❑ *Possible solution*: Use of excess borane

disadvantageous in certain cases e.g. limiting aldehyde

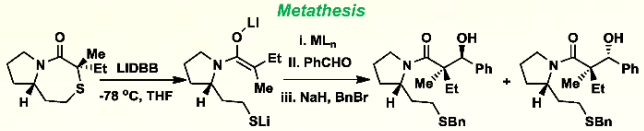
Alternate route: Metathesis



UNEXPECTED

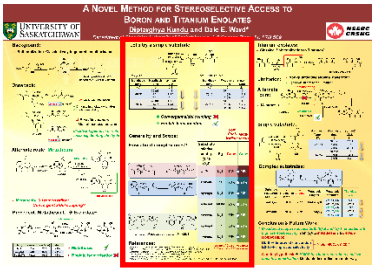
- Metathesis → *Isomerisation/ Convergent aldol coupling?*

Precedent: Metathesis Li → B enolate[4, 5]

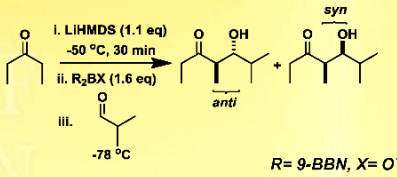


ML_n	*syn*:*anti*	de (*syn*)	yield
N/A	52:48	23%	71%
Cy_2BCl	92:8	96%	31%
Bu_2BOTf	79:21	95%	48%

- Metathesis ✓
- Enolate isomerisation ✗



Let's try a simple substrate:



R= Cy, X= Cl

Metathesis Temp.	Metathesis time	*syn:anti (Z:E)*
N/A	0	2:1
-78 °C	30 min	1:1
	1.0 h	1:3.1
	2.0 h	1:6
-50 °C	30 min	1:1.6
	1.0 h	1:5.5
	2.0 h	1:9

R= 9-BBN, X= OTf

Metathesis Temp.	Metathesis Time	*syn:anti (Z:E)*
N/A	0	2:1
-78 °C	30 min	1.5:1
	1.0 h	1:1.2
	2.0 h	1:3
-50 °C	30 min	1.1:1
	1.0 h	1:2.5
	2.0 h	1:4.5

- ***Convergent aldol coupling*** ✗
- ***Enolate Isomerisation*** ✓

Generality and Scope:

How about complex ones?

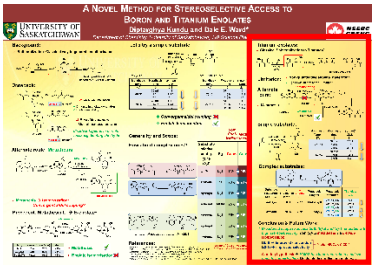
Substrate relative config. (3,4)/ (2,3)	Pg	*Soft Enol-ization** Conv.	*Meta-thesis#* Conv.
anti/----	Et_3Si	73%	95%
anti/anti	Et_3Si	70%	90%
syn/syn	Et_3Si	70%	90%
anti/syn	MOM	25%	80%
syn/anti	Et_3Si	65%	85%
syn/syn	Et_3Si	50%	90%
anti/anti	Et_3Si	35%	85%

In each of the above cases, dr=>20:1

References:

1. Paterson, I.; Tillyer, R. D. *Journal of Organic Chemistry* **1993,** *58* (16), 4182-4184.
2. Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994,** *35* (48). 9083-9086.
3. Paterson, I.; Bower, S.; Tillyer, R. D. *Tetrahedron Lett.* **1993,** *34* (27). 4393-4396.
4. Burke, E. D.; Gleason, J. L. *Organic Letters* **2004,** *6* (3), 405-4075.
5. Becerril-Jiménez, F.; Ward, D. E. *Organic Letters* **2012,** *14* (6), 1648-1651.
6. Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *Journal of the American Chemical Society* **1991**. *113* (3). 1047-1049.

**2.1 eq of Cy_2BCl was used*
#1.6 eq of Cy_2BCl was used



Titanium enolates:

➢ Classical Soft enolization to Titanates[6]:

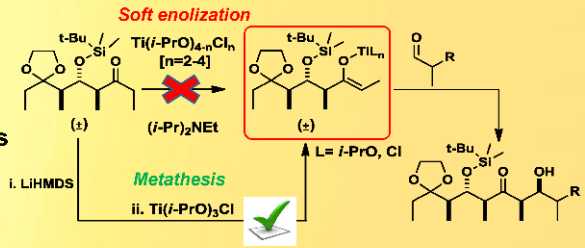
Limitation:

➢ Non-quantitative enolate generation

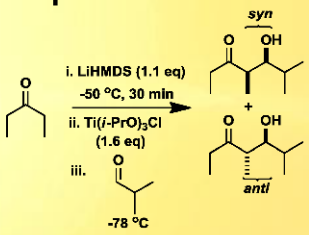
❖ High Lewis acidity of the Ti reagent

Alternate route:

➢ Metathesis

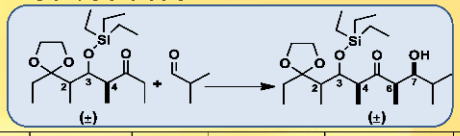


Simple substrate:



Metathesis Temp.	Metathesis time	*syn:anti* (*Z:E*)
N/A	0	2:1
-78 °C	30 min	2.5:1
	1.0 h	3.1
	2.0 h	4.8:1
-50 °C	30 min	5:1
	1.0 h	7.5:1
	2.0 h	10:1

Complex substrates:



Substrate rel. config. (3,4)/(2,3)	Li enolisation temp.	Li enolate *Z:E*	Metathesis reagent	Metathesis condition	Ti enolate *Z:E*
anti/syn	-50 °C	2.7:1	Ti(*i*-PrO)$_3$Cl	-78 °C, 1 h	5:1
				-50 °C, 1 h	>20:1
anti/anti	-78 °C	2.7:1	Ti(*i*-PrO)$_2$Cl$_2$	-50 °C, 2 h	8.9:1
				-78 °C, 2 h	>20:1
				-78 °C, 4 h	9.6:1

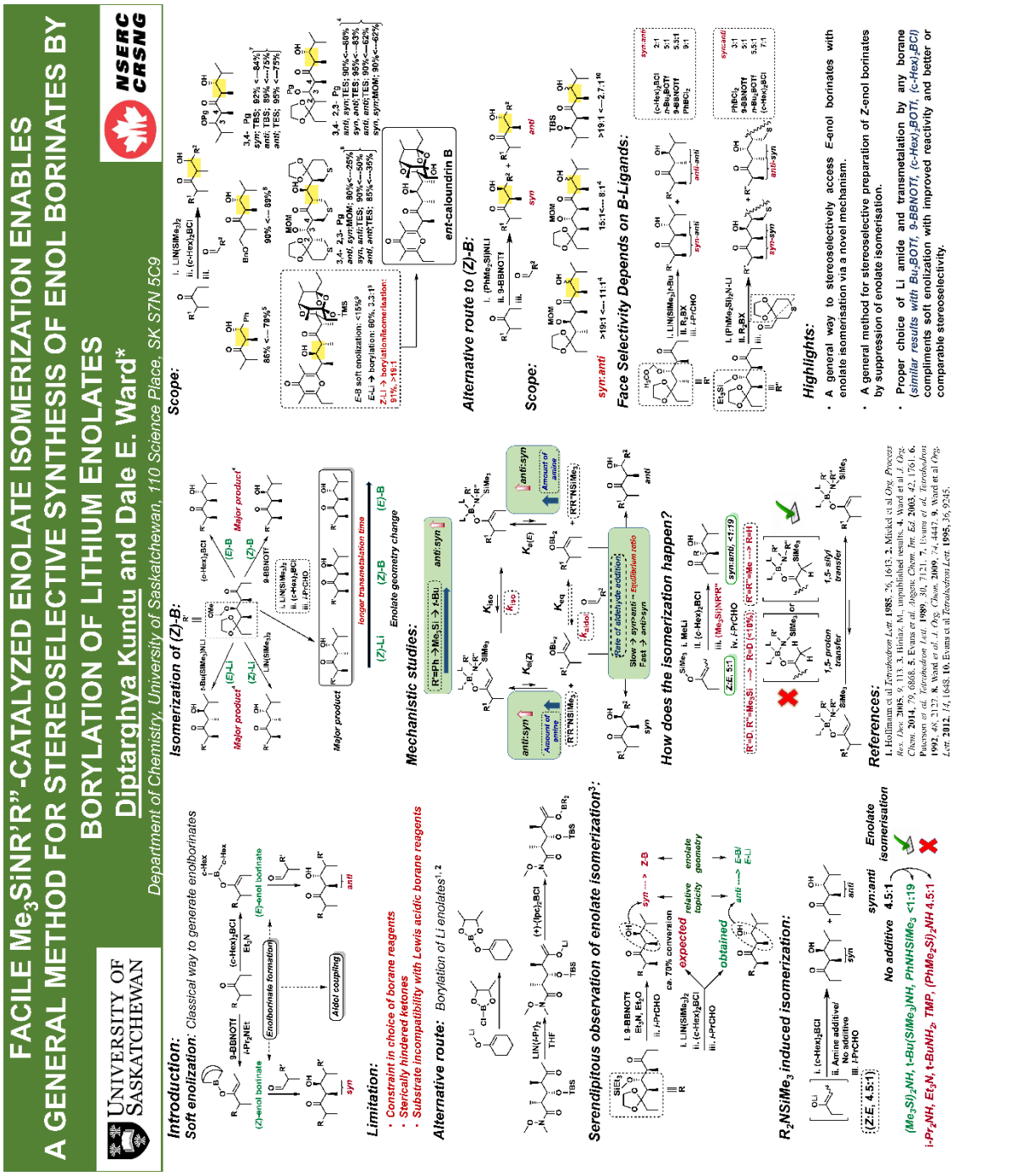
Conclusion & Future Work:

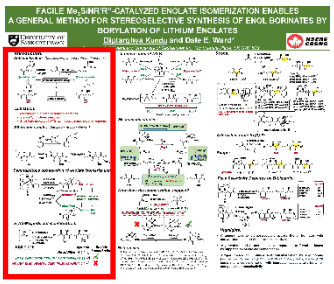
✓ *Broadened scope to access both (E)-B and (Z)-Ti enolates with high stereoselectivity* from (*Z*)-Li metathesis via *Enolate isomerisation.*

(*E*)-B → improved conversion
(*Z*)-Ti → improved selectivity
} Yield >80%, dr>20:1

✓ **Working hypothesis→** *HMDS has important role to catalyze enolate isomerisation*. Mechanistic studies are underway.

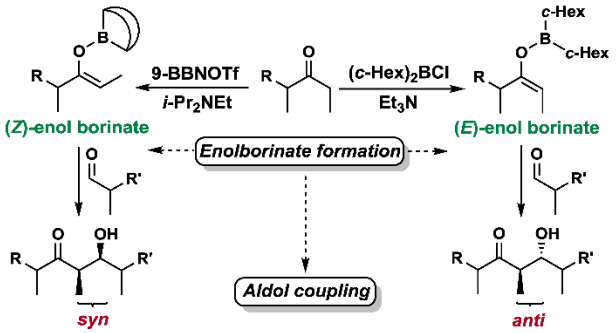
31. Kundu, D.; Ward, D. E., Facile $Me_3SiNR_1R_2$-Catalyzed Enolate Isomerization Enables a General Method for Stereoselective Synthesis of Enol Borinates by Borylation of Lithium Enolates. Presented at the International Chemical Congress of Pacific Basin Societies, Honolulu, Hawaii, USA, December 15–20, 2015.





Introduction:

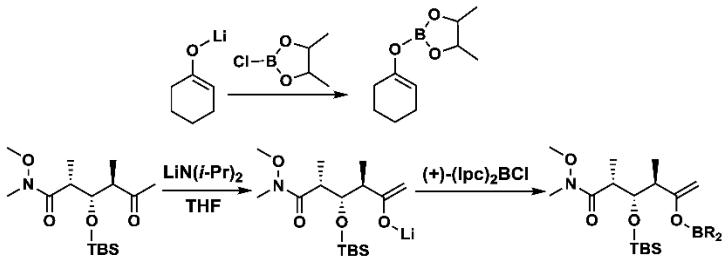
Soft enolization: *Classical way to generate enolborinates*



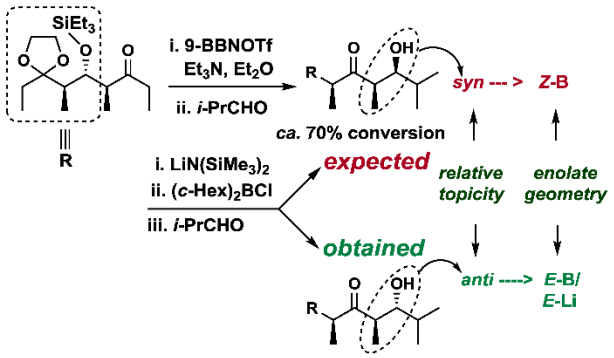
Limitation:

- ***Constraint in choice of borane reagents***
- ***Sterically hindered ketones***
- ***Substrate incompatibility with Lewis acidic borane reagents***

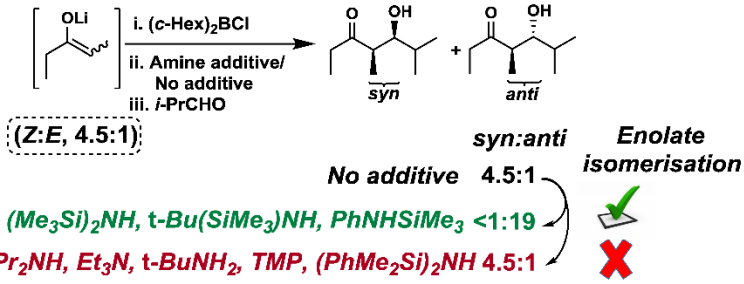
Alternative route: *Borylation of Li enolates*[1, 2]

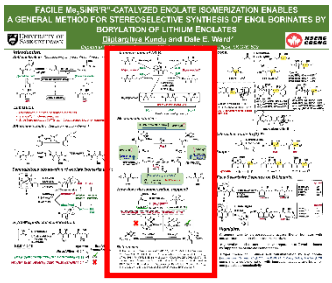


Serendipitous observation of enolate isomerization[3]:

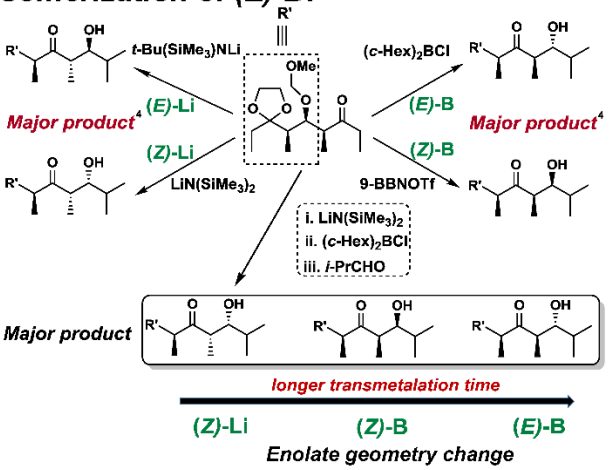


R_2NSiMe_3 induced isomerization:

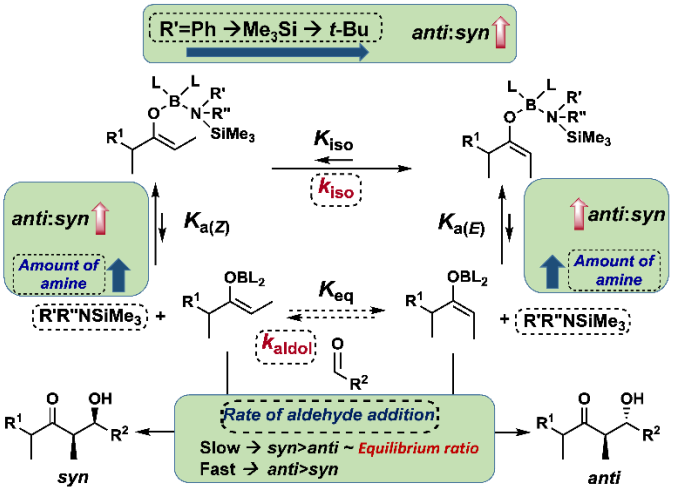




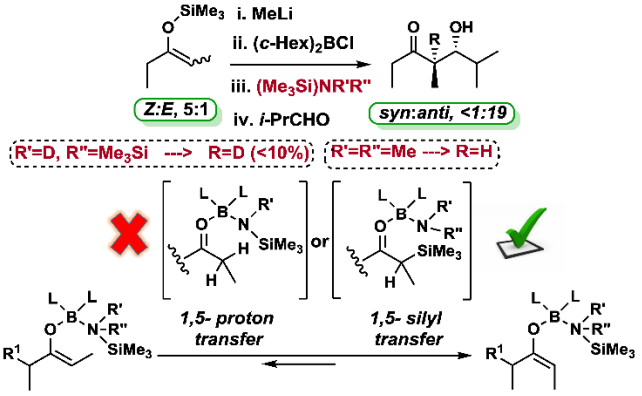
Isomerization of (Z)-B:



Mechanistic studies:

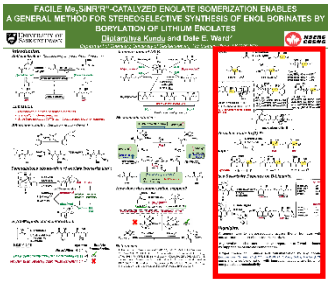


How does the isomerization happen?

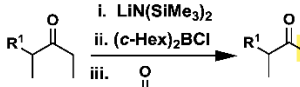


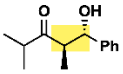
References:

1. Hoffmann et al *Tetrahedron Lett.* **1985**, *26*, 1643. **2.** Mickel et al *Org. Process Res. Dev.* **2005**, *9*, 113. **3.** Biniaz, M., unpublished results. **4.** Ward et al *J. Org. Chem.* **2014**, *79*, 6868. **5.** Evans *et al. Angew. Chem. Int. Ed.* **2003**, *42*, 1761. **6.** Paterson *et al. Tetrahedron Lett.* **1989**, *30*, 7121. **7.** Evans *et al. Tetrahedron* **1992**, *48*, 2127. **8.** Ward *et al. J. Org. Chem.* **2009**, *74*, 4447. **9.** Ward et al *Org. Lett.* **2012**, *14*, 1648. **10.** Evans et al *Tetrahedron Lett.* **1995,** *36*, 9245.

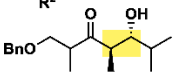


Scope:

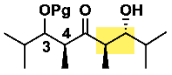




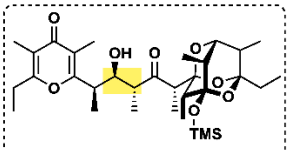
86% <--- 79%[5]



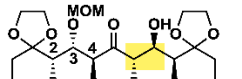
90% <--- 89%[6]



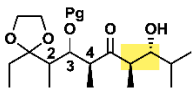
3,4- Pg
syn; TBS; 92% <---84%
anti; TBS; 89% <---75%
anti; TES; 95% <---75%[7]



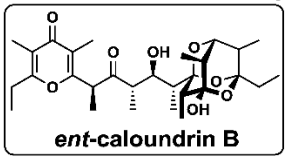
E-B soft enolization: <15%[9]
E-Li → borylation: 60%, 3.3:1[9]
Z-Li → borylation/isomerisation: 91%, >19:1



3,4- 2,3- Pg
anti, syn;MOM; 80%<---25%
syn, anti;TES; 90%<---50%
anti, anti;TES; 85%<---35%[8]

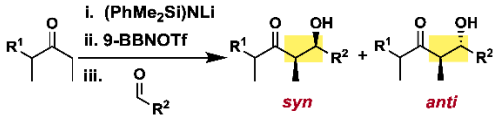


3,4- 2,3- Pg
anti, syn;TES; 90%<---80%
syn, anti;TES; 95%<---83%
anti, anti;TES; 90%<---62%
syn, syn;MOM; 90%<---62%[4]

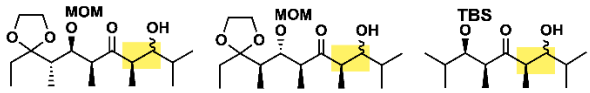


ent-caloundrin B

Alternative route to (Z)-B:

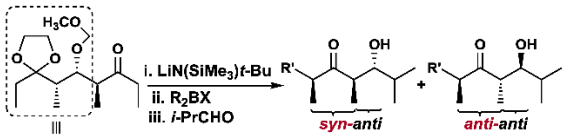


Scope:

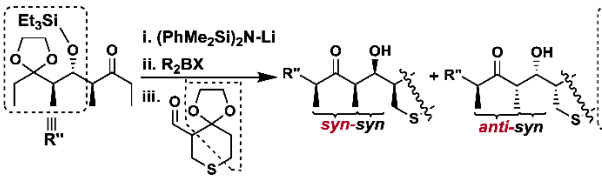


syn:*anti* >19:1 <--- 11:1[4] 15:1<--- 8:1[4] >19:1 <---2.7:1[10]

Face Selectivity Depends on B-Ligands:



	syn:*anti*
(c-Hex)$_2$BCl	2:1
n-Bu$_2$BOTf	5:1
9-BBNOTf	5.5:1
PhBCl$_2$	9:1



	syn:*anti*
PhBCl$_2$	3:1
9-BBNOTf	5:1
n-Bu$_2$BOTf	5.5:1
(c-Hex)$_2$BCl	7:1

Highlights:

- A general way to stereoselectively access *E*-enol borinates with enolate isomerisation via a novel mechanism.
- A general method for stereoselective preparation of *Z*-enol borinates by suppression of enolate isomerisation.
- Proper choice of Li amide and transmetalation by any borane (*similar results with Bu$_2$BOTf, 9-BBNOTf, (c-Hex)$_2$BOTf, (c-Hex)$_2$BCl*) compliments soft enolization with improved reactivity and better or comparable stereoselectivity.